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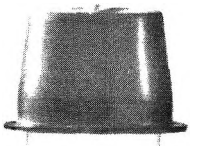

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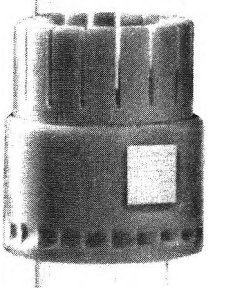

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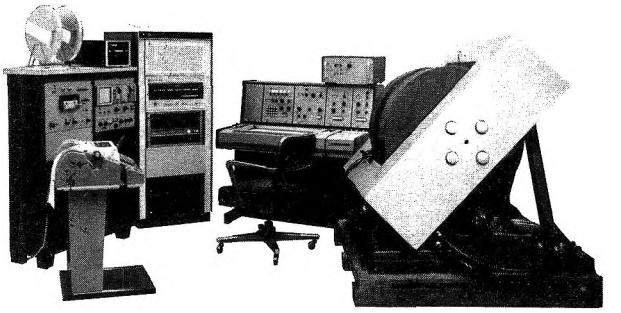

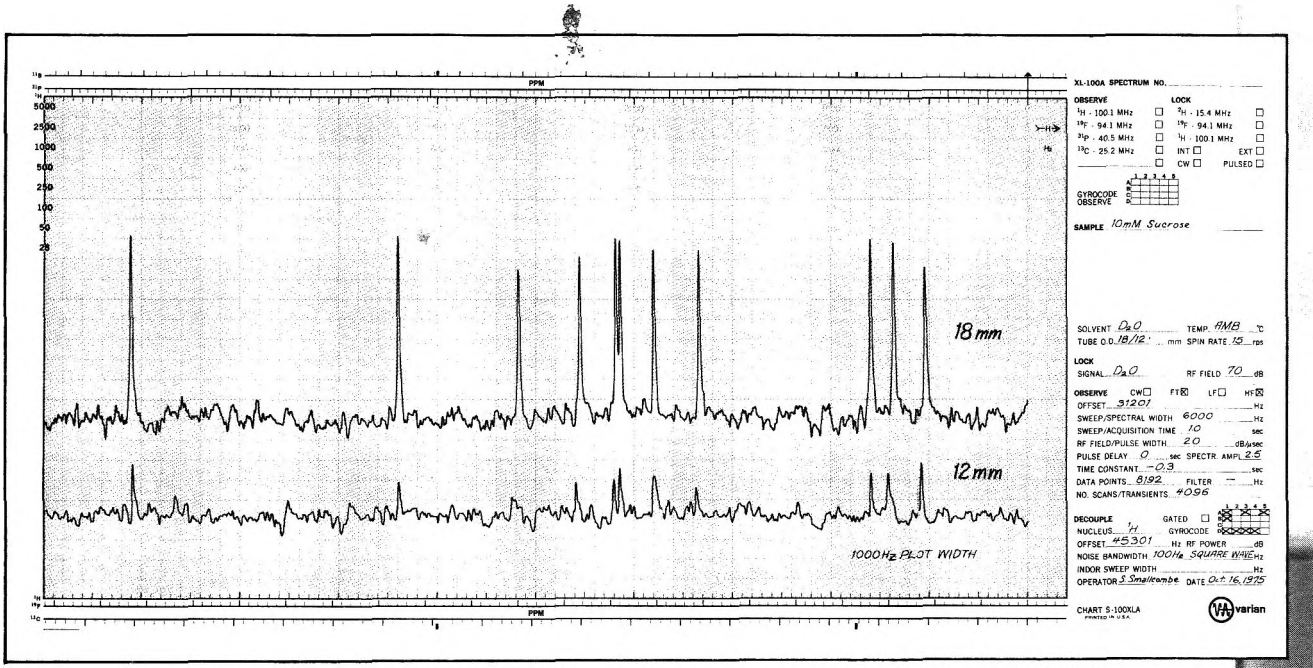

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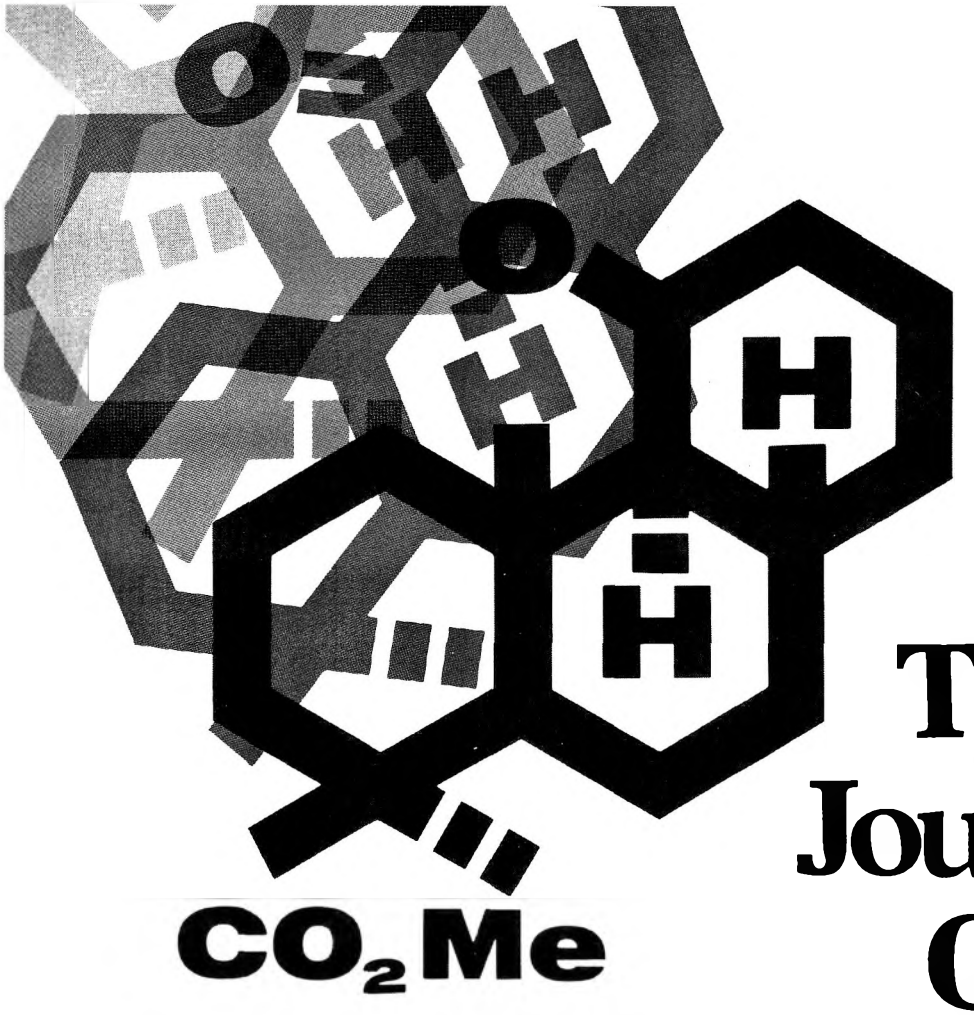

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Acid-Catalyzed Hydration of Dienes. 2. Changes in Activity Coefficient Ratios, Enthalpy, and Entropy as a Function of Sulfuric Acid Concentration

J. L. Jensen,* V. Uaprasert, and C. R. Fujii

Department of Chemistry, California State University, Long Beach, California 90840

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Acidity and temperature dependence of rates of hydration and equilibrium ratios for hydration of 1,3-cycloalkadienes are reported over the acidity range 0.5–10.3 M H_2SO_4. $\Delta H^{\ddagger}$ decreases by 9 kcal mol^{-1} and $\Delta S^{\ddagger}$ decreases by 12 eu over the acid range 0.5–5.6 M H_2SO_4. Above 5.6 M H_2SO_4 the decrease in $\Delta G^{\ddagger}$ is due almost solely to $\Delta S^{\ddagger}$ increasing by 20 eu. Plots of $\Delta H^{\ddagger}$ vs. $\Delta S^{\ddagger}$ are linear with slopes (β) of 670 and 80 over the respective acidity ranges. Changes are ascribed to a dielectric solvation effect in dilute acid being overcome by increasing solvent structure as availability of water decreases below 7:1 H_2O:H_2SO_4 mole ratio. Kinetic acidity dependence is consistent with significant but incomplete proton transfer in the transition state for hydration. Acidity dependence of the equilibrium ratio is not described by known combinations of acidity functions H_R, H_C, and/or H_{ROH}, suggesting that triaryl carbinols are poor models for 2-cycloalkenols regarding activity coefficient behavior. Evidence is presented indicative of alcohol protonation becoming significant in about 40% H_2SO_4, provided the quantity $a_{H^+}f_D/f_{ROH_2^+}$ is nearly independent of acidity—this requires that $f_D/f_{ROH_2^+}$ decrease be dramatic. ΔG is nearly independent of acidity; however, ΔH and ΔS change in exactly the same manner as $\bar{C}_p$ (solv) and all exhibit a minimum value at H_2O:$H_2SO_4 \simeq 7:1$.

An excellent recent review observes that sulfuric acid solutions as solvent for acid-catalyzed reactions demonstrate properties which are unparalleled in toto by any other single acid medium.[1] It is for this reason that more data exist for reactions in moderate to concentrated sulfuric acid than for any other mineral acid. However, in many ways H_2SO_4 solutions are far from the ideal acidic medium. In addition to the often noted tendency of concentrated H_2SO_4 solutions to sulfonate or oxidize solutes, the thermodynamic properties of the solvent change markedly with changing acid concentration. There exist several cases where, for example, pK_a data are obtained in H_2SO_4 (using an acidity function treatment) and only later is it observed that totally different results are obtained in $HClO_4$.[2] Often the cause of "anomalous" behavior in H_2SO_4 solutions has not been determined. For these reasons we wish to report on a thermodynamic study of a reaction previously investigated in $HClO_4$ solution.[3] That closely similar behavior in $HClO_4$ and H_2SO_4 solutions is found confirms the assumption that sulfonation or oxidation reactions do not compete with the reaction of interest.

Of particular relevance to our study are the changes in solvent molar energy terms with increasing H_2SO_4 concentration.[4] To our knowledge, no explanation has been proffered for these changes, in terms translatable to influencing an acid-catalyzed reaction rate. The method employed in this report is to establish whether changes in enthalpy and entropy as determined by kinetic and equilibria studies parallel changes in solvent enthalpy or entropy terms. The conclusion suggested is that although the nature of the solvent is changing markedly, measured changes in enthalpy and entropy of activation are explainable simply in terms of medium effects on a chemical reaction.

Previous discussions of the acidity dependence of reactions in acid media have been limited to the acidity function treatment, which allows discussion of changes in free energies as indicated by changes in activity coefficient ratios.[1,5] The present study discusses entropic and enthalpic contributions. The rather smooth overall changes in free energies observed arise from compensating changes in enthalpy and entropy terms.

Experimental Section

Materials and Kinetic Method. Substrates were obtained from Aldrich Chemical Co. and were molecularly distilled. The procedure for 1,3-cyclohexadiene has been described previously.[3] 1,3-Cyclooctadiene was more conveniently handled as ca. 10^{-2} M solution in ethanol; concentrations of ethanol in final kinetic solutions of acid were ≤5% and did not affect the reaction rate significantly. The general kinetic method was that reported earlier.[3]

Product Analysis. The reaction being studied is eq 1. That the product is indeed 2-cycloalkenol rather than a diol was confirmed (as in an earlier study)[3] by noting that (a) products exhibited a strong short-wavelength absorbance and (b) corresponding cycloalkenes are not measurably hydrated nor are cycloalkanols dehydrated under conditions used in this study. k_{obsd} for 1,3-cyclohexadiene in 2.56 M H_2SO_4 at 80 °C is $>10^4$ that of cyclohexene.[7] Both observations support the rapid reversible hydration of 1,3-cycloalkadienes in acidic media to form 2-cycloalkenols (eq 1).

Attempts to extend conditions reported in Table I (higher acidities and temperatures) failed because of the incursion of other, as yet uncharacterized, reactions. For example, 1,3-cyclohexadiene and 1,3-cyclooctadiene upon standing for 15–20 half-lives in >6 M H_2SO_4 yielded pink and yellow solutions. These reactions are presumably

Table I. Values of k_{obsd} and Equilibrium Ratios ([Prod]/[Reactant])[a]

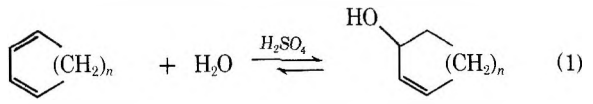
$M_{H_2SO_4}$	$10^4 k_{obsd}$		[2-cycloalkenol]/[1,3-cycloalkadiene]	
		20 °C		
4.04	6.16		5.82	
5.64	54.9		12.6	
10.3		30.4		2.90
		30 °C		
4.04	16.2		8.76	
5.64	148		13.7	
9.21		13.2		3.07
10.3		92.4		5.08
		40 °C		
2.56	8.27		4.23	
4.04	50.6		6.31	
5.64	359		12.8	
7.02		1.29		2.88
8.00		5.49		3.59
9.21		43.2		4.87
10.3		262		7.51
		50 °C		
1.05	2.34		3.43	
2.56	23.4		4.47	
4.04	114		7.28	
7.02		3.79		3.93
8.00		17.3		5.28
9.21		111		8.01
		60 °C		
0.51	2.33			2.45
1.05	8.66		2.46	
2.56	59.8		4.24	
4.04	246		5.59	
5.64		1.22		3.55
7.02		9.99		4.74
8.00		45.8		5.61
9.21		255		11.1
		70 °C		
0.51	8.46		1.92	
1.05	25.0		2.65	
2.56	157		4.45	
4.04	678		8.72	
5.64		2.90		4.29
7.02		27.8		5.62
8.00		116		8.35
9.21		492		16.4
		80 °C		
0.51	23.0		1.99	
1.05	60.9		2.56	
2.56	311	.52	4.98	.68
4.04		1.59		1.53
5.64		6.15		4.77
7.02		41.6		5.96
8.00		195		13.6

[a] Mean values measured at λ_{max} of diene; average deviation of replicate measures ≤ 5%.

linked to the increasing concentration of cycloallylic ions as sulfuric acid concentration increases.[8-10] The uv-visible spectra of these solutions evidenced broad multiple absorption bands over the entire range 500–200 nm; further discussion of these kinetic results is deferred to a time when the reaction products can be characterized. *All* data within Table I reflect clear hydration–dehydration over 8–10 half-lives of reaction time; i.e., data reported in Table I are for eq 1.

Results

The reactions investigated are reversible and at equilibrium the product concentration is generally greater than that of reactant. Pseudo-first-order rate constants were obtained in



(1)

1,3-cycloalkadiene 2-cycloalkenol

the traditional manner[3] by following decreasing absorbance at λ_{max} of cycloalkadiene; linear first-order kinetic plots were obtained for 3 half-lives (or longer) of reaction time. Since reactant (1,3-cycloalkadiene) is the only species absorbing light significantly at the wavelengths used to follow the reaction, calculation of the equilibrium ratio is considerably simplified.

$$\frac{[\text{2-cycloalkenol}]}{[\text{1,3-cycloalkadiene}]} = \frac{A_0 - A_e}{A_e} \tag{2}$$

where A_0 = absorbance at time zero, A_e = absorbance at equilibrium (i.e., at time "infinity") and concentrations of species refer to the equilibrium state.

Normally $A_0 - A_e$ can be obtained most accurately by extrapolating the first-order rate plot back to zero time (i.e., time of mixing); however, for slower reactions particularly, the same value can be obtained by measuring A_0 immediately upon mixing.

Having measured the pseudo-first-order observed rate constant and the equilibrium ratio, the rate constant for hydration may be calculated using the following relationships.[11]

$$k_{obsd} = k_{hyd} + k_{dehyd} \tag{3}$$

$$\frac{[\text{2-cycloalkenol}]}{[\text{1,3-cycloalkadiene}]} = \frac{k_{hyd}}{k_{dehyd}} \tag{4}$$

where k_{hyd} = rate constant for the forward reaction in eq 1 and k_{dehyd} = rate constant for the reverse reaction in eq 1.

In most instances the equilibrium ratio is considerably greater than unity and therefore k_{hyd} is more precisely defined than k_{dehyd} (i.e., k_{dehyd} is the small difference between the two larger rate constants, k_{obsd} and k_{hyd}, in eq 3). As a consequence, this paper for the most part discusses effects of structure and solvent on rate constants for hydration.

Thermodynamic Parameters. Usual treatment of the *dependence of* k_{hyd} on *temperature*[3] yields enthalpies and entropies of activation. Table II displays values resulting from a least-squares analysis of the data. Values are in a range typical for alkene hydration.[3]

Since equilibrium ratios in Table I are of a size allowing precise measurement (≤ ±5% for $K \leq 10$), thermodynamic parameters for equilibrium 1 were calculated using eq 5.

$$\Delta H - T\Delta S = -RT \ln \frac{[\text{2-cycloalkenol}]}{[\text{1,3-cycloalkadiene}]} \tag{5}$$

Of course, the same thermodynamic parameters are obtainable by treating k_{dehyd} (from eq 3 and 4) in the traditional way and comparing activation parameters for hydration and dehydration. Use of eq 5 is more direct since equilibrium 1 is discussed in a subsequent section; however, it must be remembered that a standard deviation of ±0.5 kcal/mol for $\Delta H^{\ddagger} \simeq 25$ kcal/mol is a different order of precision than ±1 kcal/mol for $\Delta H = 0.5$ kcal/mol. That is, although equilibrium ratios and rate constants can be measured with comparable precision, the former is *much* less sensitive to changes in temperature (i.e., $\Delta H < \Delta H^{\ddagger}$). This is just another way of stating that ΔH is the rather small difference between two much larger $\Delta H^{\ddagger}$ values, those for hydration and dehydration. In general, the same conclusions hold for ΔS as well.

For our discussion, use of ‡ denotes $\Delta H^{\ddagger}$ and/or $\Delta S^{\ddagger}$ cal-

Table II. Thermodynamic Parameters[a]

1,3-Cyclohexadiene					1,3-Cyclooctadiene				
$M_{H_2SO_4}$	ΔH^c	$\Delta H^{\ddagger b}$	ΔS^c	$\Delta S^{\ddagger b}$	$M_{H_2SO_4}$	ΔH^c	$\Delta H^{\ddagger b}$	ΔS^c	$\Delta S^{\ddagger b}$
0.51	−3.5	25.1	−9	−1.1	4.04		20.8		−17.4
1.05	−3.0	23.3	−7	−3.6	5.64	3.5	19.0	13	−20.6
2.56	1.0	19.8	6	−10.0	7.02	4.1	19.8	15	−13.8
4.04	0.4	18.0	5	−12.2	8.00	6.8	20.3	24	−9.1
5.64	0	16.5	5	−12.9	9.21	8.6	19.3	31	−8.5
					10.3	8.7	20.7	32	−0.2

[a] Calculated at 25 °C, standard deviation in enthalpies and entropies ≤0.5 kcal mol^{-1} and ≤2 eu, respectively. [b] Calculated from pseudo-first-order rate constants for hydration (eq 3 and 4 and ref 1). [c] Calculated from equilibrium ratios (eq 2 and 5), standard deviations in enthalpies and entropies ≤1 kcal mol^{-1} and ≤4 eu, respectively.

culated from rate data; *absence* of ‡ denotes ΔH and/or ΔS calculated from equilibrium data. Use of $\Delta H°$ and/or $\Delta S°$ is avoided, since none of our data can be related meaningfully to standard state.

Acidity Dependence. Earlier rigorous discussions of acidity dependence of olefin protonation and hydration[12-14] presumably applies to these reactions as well, and therefore extensive comment as to whether H_0 is an appropriate acidity function is unnecessary. Suffice it to say that plots are reasonably linear over the acidity ranges studied and that slopes, $d(\log k_{hyd})/-d(-H_0)$, approximate unity.

Our data was also plotted against H_C, a recently defined acidity function based on protonation of carbon bases (mainly substituted azulenes).[15] While fairly linear, $d(\log k)/d(-H_C) \simeq 0.6$, and thus it appears that H_0 is still as good or better for describing the acidity dependence of rate-controlling proton transfer to olefins as any acidity function available. Use of H_0 has certain advantages, since it has been more widely studied and thus is the most closely defined acidity function. Of particular relevance to our study is the change in H_0 with increasing temperature. $d(-H_0)/d(T)$ has recently been defined:[16] using these values for H_0, $d(\log k)/d(-H_0) \simeq 1.3$ in moderately concentrated sulfuric acid solutions. Although plots of $-H_0$ vs. $\log k_{hyd}$ are reasonably linear, there appears to be slight upward curvature with increasing acid concentration [i.e., $d(\log k)/d(-H_0) \simeq 1.1$ in dilute acid solution, 0.5–3 M]. While $d(-H_0)/dT$ is a significant quantity, it changes rather regularly with both increasing temperature and increasing acid concentration; thus using H_0 values at 25 °C[16-18] to correlate rate data obtained at 80 °C $d(\log k)/d(-H_0) = 1.05$; using H_0 values at 80 °C[16] the plot curvature is about the same and $d(\log k)/d(-H_0) = 1.15$. The conclusion is, then, that in a few marginal cases temperature effects on acidity dependence may lead to erroneous conclusions, but the approximate nature of $d(\log k)/d(-H_0)$ correlations precludes serious complications.

The cause of decreasing H_0 with increasing temperature is interesting. A significant amount of the change (20–40%) is attributable to changing concentration of H_2SO_4 as the temperature is increased; i.e., $\rho^{25}/\rho^{100} = 1.04$.[16] Since correlations of H_0 and/or $\log k$ with, say, $[H_2SO_4]$ always refer to $[H_2SO_4]$ as titrated at 25 °C, rate data obtained at 100 °C in x M H_2SO_4 *should*, for appropriate correlation, correlate with H_0 values at 25 °C for $0.96x$ M H_2SO_4. As mentioned above, however, such corrections are sufficiently minor as to be unwarranted. The rest of the change of H_0 with increasing temperature (the majority) must lie in the activity term of the definition. This is corroborated by the fact that $d(-H_0)/dT \neq d(-H_R)/dT$.[16,19] For example, 2% H_2SO_4 behaves 0.10 H_R units and 0.03 H_0 units *weaker* an acid at 45 °C, whereas 70% H_2SO_4 behaves 0.49 H_R units *stronger* and 0.35 H_0 units *weaker* an acid at 45 °C.[16,19] Clearly differences in temperature dependence of acidity functions become increasingly significant as acid concentration increases. The consequence of this result is clear: *differences* in acidity function behavior can only be discussed near 25 °C or for cases where the temperature dependence of the acidity function is known. For this reason, our later discussion of $H_R - H_C$ is in reference only to data at ≤40 °C.

One further point requires brief elaboration. Variation of H_0 with temperature may be expressed as $d(-H_0)/d(1/T)$ and is thus incorporated into the experimental $\Delta H^{\ddagger}$ value. Fortunately $d(-H_0)/d(1/T)$ values are known to be small.[16] The maximum effect in our study is in 10.3 M H_2SO_4 where $d(-H_0)/d(1/T) = 1.28 \times 10^{-3}$ deg^{-1} and $d(\log k)/d(-H_0) \simeq 1.4$; the corresponding maximum contribution to $\Delta H^{\ddagger}$ is 8×10^{-6} kcal mol^{-1}. Consequently, all such insignificant contributions to $\Delta H^{\ddagger}$ are ignored.

Discussion

The mechanism of hydration of 1,3-cycloalkadienes has been proposed as in Scheme I,[3,20] where . . . refers to partial bonding, D designates 1,3-cycloalkadiene, DH^+ designates cycloallylic carbonium ion intermediate, ROH_2^+ designates protonated 2-cycloalkenol, and ROH designates 2-cycloalkenol.

As developed elsewhere,[3,20] the extent of D–H bond formation in tr^+ is significant, but not complete. Thus in subsequent discussions relating to solvation of tr^+, the solvation energy of tr^+ is found to be closer to that for alcohols than to the very large solvation energy for protonated alcohols.

It is assumed throughout our discussion that medium dependence of hydration of 1,3-cyclohexadiene is essentially equal to that of 1,3-cyclooctadiene; i.e., the solvation energy of tr^+ is reasonably similar for these two compounds. This rational assumption is experimentally corroborated by data in Table II: heats and enthalpies of hydration, while not equal, change comparably over the range 4–6 M H_2SO_4.

Kinetic Acidity Function Treatment. The quantity $d(\log k_{hyd})/d(M_{H_2SO_4})$ is greater than $d(-H_0)/d(M_{H_2SO_4})$ and less than $d(-H_R)/d(M_{H_2SO_4})$. Thus, as observed previously for other olefin hydrations, the activity ratio term f_D/f_{tr^+} increases relative to f_B/f_{BH^+} and decreases relative to f_{ROH}/f_{R^+} or f_C/f_{CH^+}.

$$k_{hyd} = k_1 a_{H^+} f_D / f_{tr^+} \quad (6)$$

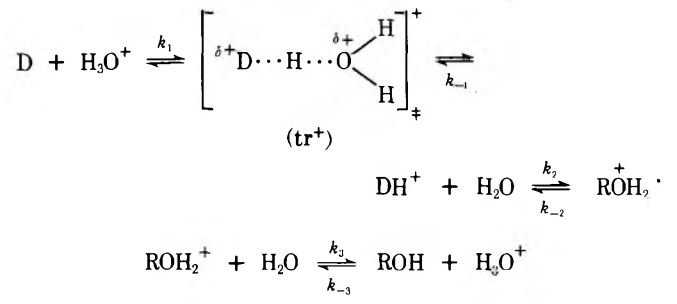
$$H_0 \equiv -\log a_{H^+} f_B / f_{BH^+} \quad (7)$$

$$H_R \equiv -\log (a_{H^+}/a_{H_2O})(f_{ROH}/f_{R^+}) \quad (8)$$

$$H_C \equiv -\log a_{H^+} f_C / f_{CH^+} \quad (9)$$

where k_{hyd} = experimental rate constant for hydration of 1,3-cycloalkadienes, k_1 = thermodynamic rate constant for rate-controlling proton transfer to 1,3-cycloalkadiene, a_{H^+} = activity of "proton", f_D = activity coefficient of 1,3-cycloalkadiene, f_{tr^+} = activity coefficient of the transition state for 1,3-cycloalkadiene hydration. H_0, H_R, and H_C are acidity functions based on anilinium ion (BH^+),[17] and aryl carbinol (ROH)[24] ionization and azulene (C) protonation,[15] respectively.

Scheme I



This is perhaps most easily understood in terms of a greater solvation requirement for tr^+ than for CH^+, but less than for BH^+ (although to be precise, this statement *must* be made relating f_{tr^+} to f_D, f_{CH^+} to f_C, and f_{BH^+} to f_B, since it is improbable that f_D changes with increasing acidity just as f_C or f_B).[25] The conclusion reached, then, is that tr^+ is solvated more than a carbonium ion but less than a primary anilinium ion, which is, of course, consistent with the structure of tr^+ given in Scheme I incorporating a H_3O^+/H_2O intermediate species partially bonded to the 1,3-cycloalkadiene. A further conclusion regarding extent of proton transfer is implied by noting that activity coefficient ratios change with increasing acidity according to the order $f_{ROH}/f_{R^+} > f_C/f_{CH^+} > f_D/f_{tr^+} > f_B/f_{BH^+} \gg f_{ROH}/f_{ROH_2^+}$, where the latter ratio refers to the recently defined acidity function for ethanol protonation, H_{ROH}.[21] This order is only consistent with tr^+ having significant proton transfer; i.e., tr^+ does *not* possess sites of such great solvation energy as ROH_2^+ possesses and thus a significant lessening of positive charge on oxygen is indicated in tr^+. This is in agreement with the solvent isotope effect $k_{H_2O}/k_{D_2O} = 2.3$[20] and the measured Bronsted α of 0.7–0.8 for hydration of isobutylene[23] and styrenes.[14,22]

Equilibrium Acidity Function Treatment. Dependence of the equilibrium ratio (4) on acidity is rather complex, but suggests that *if* alcohols are protonated in ≤10 M H_2SO_4 solution, the activity coefficient $f_{ROH_2^+}$ must be *dramatically* medium dependent. Under our experimental conditions, the equilibrium ratio measured using eq 4 and Scheme I is

$$\frac{[ROH] + [ROH_2^+]}{[D]} = \frac{k_1k_2k_3}{k_{-1}k_{-2}k_{-3}} a_W f_D/f_{ROH} + \frac{k_1k_2}{k_{-1}k_{-2}} a_{H^+} \frac{f_D}{f_{ROH_2^+}} \quad (10)$$

In very dilute acid, ROH_2^+ terms drop out and the equilibrium ratio should change as $a_W f_D/f_{ROH}$. Several measurements given in Table I show the equilibrium ratio in 0.5 and 1 M H_2SO_4 to be virtually equal (as eq 10 predicts, since $a_W f_D/f_{ROH}$ is nearly constant over that region). By comparing acidity functions, it is possible to see quantitatively how terms similar to those in eq 10 behave. Using definitions given by eq 8, 9, and 11

$$H_{ROH} \equiv -\log a_{H^+} f_{EtOH}/f_{EtOH_2^+} \quad (11)$$

$$H_R - H_C = \log (a_W f_C/f_{ROH}) \quad (12)$$

$$H_R - H_C - H_{ROH} - \log a_W = \log (a_{H^+} f_C/f_{EtOH_2^+}) \quad (13)$$

Equations 12 and 13 do not show log (f_{R^+}/f_{CH^+}) and log (f_{EtOH}/f_{ROH}) terms, since it is customary to assume that changes in these terms are minimal relative to changes in eq 12 and 13; i.e., medium dependence of protonated azulene CH^+ and triaryl carbonium ions is comparable, as is that of ethanol and triaryl carbinols. Table III lists these quantities along with log (equil ratio), eq 10. *Provided* that azulenes are good models for 1,3-cycloalkadienes, triaryl carbinols are good models for 2-cycloalkenols, and protonated ethanol is a good model for protonated 2-cycloalkenols, log (equil ratio) should decrease somewhat (according to $H_R - H_C$) until protonation of 2-cycloalkenol becomes significant, at which time a slight leveling off should be observed (according to $H_R - H_C - H_{ROH} - \log a_W$). Clearly log (equil ratio) does not behave as predicted by the H_R, H_C, and/or H_{ROH} functions; however, the behavior is as close as could be expected considering what is now known about the above "customary assumptions". Yates has recently compiled data demonstrating that even among solutes of similar charge or functional grouping, activity coefficient behavior is a complex function of dielectric, solvation, and bulk effects.[25] Therefore the data in Table III are suggestive of minimal changes in log ($a_W f_C/f_{ROH}$) and log ($a_{H^+} f_C/f_{ROH_2^+}$) terms, which is consistent with the observed changes in log (equil ratio). Qualitatively, it is surprising that log (f_C/f_{ROH}) decreases with increasing acidity; the data compiled by Yates shows the quantity $f_{benzene}/f_{benzyl\ alcohol}$ increasing with increasing acidity. Before any data of the type in Table III (excluding our experimental data) can be discussed semiquantitatively, more data similar to the compilation by Yates is required.

Table III. Activity Coefficient Behavior of Olefins, Alcohols, and Protonated Alcohols

$M_{H_2SO_4}$	Log ($a_W f_D/f_{ROH}$)[a]	Log ($a_{H^+} f_C/f_{EtOH_2^+}$)[b]	Log (equil ratio)[c]
0.51	−0.10 (−0.09)		
1.05	−0.14 (−0.12)		
2.56	−0.49 (−0.42)		−0.14 (−0.07)[d]
4.04	−0.81 (−0.66)	0.20	0.04 (0.18)[d]
5.64	−1.01 (−0.73)	0.39	0.34 (0.62)[d]
7.02	−1.02 (−0.58)	0.74	0.46 (0.89)
8.00	−1.34 (−0.76)	0.69	0.56 (1.14)
9.21	−1.65 (−0.85)	0.75	0.69 (1.49)
10.3	−2.01 (−0.96)	0.76	0.88 (1.92)

[a] $H_R - H_C$, eq 12 in text. Numbers in parentheses are $H_R - H_C - \log a_W = \log f_C/f_{ROH}$. [b] $H_R - H_C - H_{ROH} - \log a_W$, eq 13 in text. [c] Equation 10 of text. Values in parentheses are log (equil ratio) − log a_W. [d] Values normalized to fit on 1,3-cyclooctadiene scale; value of 2.2 for equilibrium ratio in 5.64 M H_2SO_4 was obtained by extrapolation of 1,3-cyclooctadiene values in Table I.

The conclusion from data in Table III is that no acidity function or combination of acidity functions adequately describes changes in the equilibrium ratio. *Qualitatively*, it appears that f_D/f_{ROH} increases somewhat with increasing acidity, but that the quantity $a_{H^+} f_D/f_{ROH_2^+}$ is rather insensitive to acidity (which requires the latter activity coefficient ratio to decrease dramatically as acidity is increased). This accounts for the difficulty encountered in actually observing protonation of alcohols by the several methods attempted:[26–32] protonation occurs over such a broad range of acidity that accompanying medium effects are truly massive. Data in Table III are consistent with protonation of 2-cycloalkenols becoming significant in 5.64 M (42%) H_2SO_4.

Enthalpy and Entropy Changes. Thermodynamic data have been reported for H_2SO_4 solutions as partial molal quantities; i.e., $\bar{C}_P$ (H_2SO_4) and $\bar{C}_P$ (H_2O) and $\bar{S}$ (H_2SO_4) and $\bar{S}$ (H_2O). However, quantities actually measured are, of course, those of the solvent. However, H_2SO_4 solutions are *not* merely mixtures of H_2SO_4 and H_2O molecules, but rather complex mixtures of H_2SO_4, HSO_4^-, H_3O^+, $H_9O_4^+$, H_2O, etc., and of a composite nature varying with acid concentration. Therefore we preferred to use quantities $\bar{C}_P$ (solv) and $\bar{S}$ (solv) which refer to experimental quantities obtained by others but reported differently by them. Figure 1 shows changes in solvent heat capacity and entropy. The complex change in $\bar{C}_P$ (solv) is truly remarkable and well outside experimental error. Simplistically, Figure 1 shows that *if* there were a mechanism

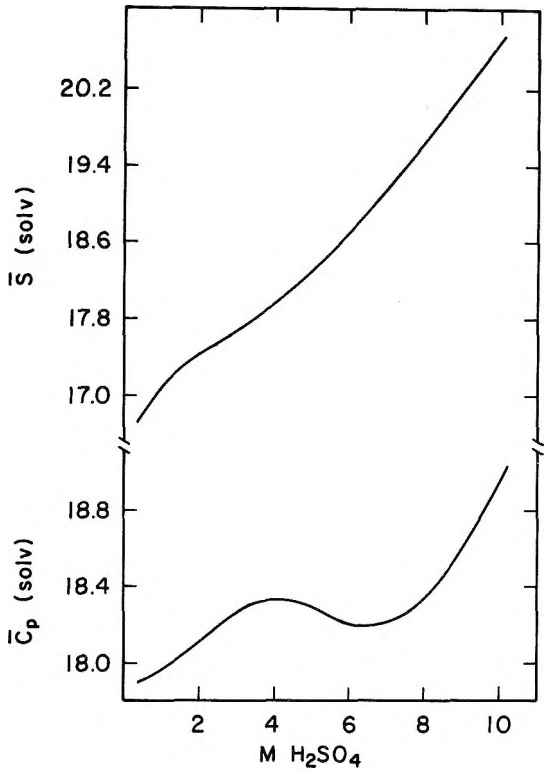


Figure 1. Plot of solvent entropy ($\bar{S}_{solvent}$, cal/deg mol solvent, top portion) and solvent heat capacity ($\bar{C}_P$ (solvent), cal/deg mol solvent, bottom portion) vs. molarity of sulfuric acid in water. Data calculated from ref 4, 1 mol of solvent ≡ (X mol H_2O + Y mol H_2SO_4)/(X + Y).

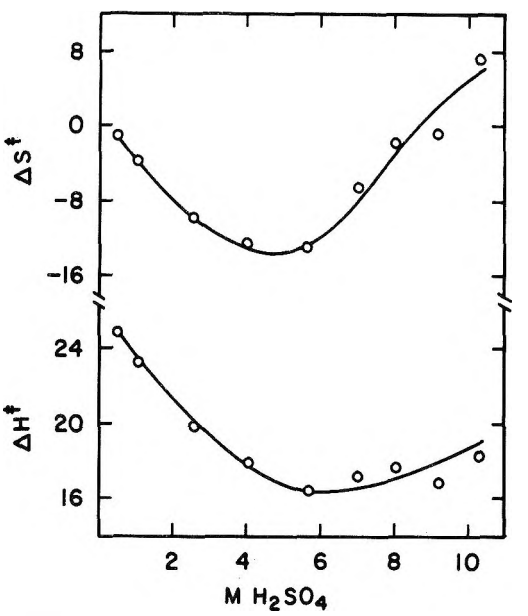


Figure 2. Plot of entropy of activation ($\Delta S^{\ddagger}$, cal/deg mol, top portion) and enthalpy of activation ($\Delta H^{\ddagger}$, kcal/mol, bottom portion) vs. molarity of sulfuric acid in water. Smooth curve represents data in Table II, considering error limits and normalizing $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for 1,3-cyclooctadiene to scale for 1,3-cyclohexadiene (e.g., $\Delta H^{\ddagger}$ plotted ≥5.6 M H_2SO_4 = $\Delta H^{\ddagger}$ (1,3-cyclooctadiene) − 2.5 kcal mol^{-1}. The amount 2.5 kcal mol^{-1} is the difference between the $\Delta H^{\ddagger}$ values for the two compounds at the common acid molarity 5.64 M).

for the solvent to transfer energy from the heat term directly toward progress on the enthalpy reaction coordinate, 4 M H_2SO_4 would have a lower $\Delta H^{\ddagger}$ than 1 M H_2SO_4 by an amount well within our experimental error (±500 cal mol^{-1}). Consequently this *direct* energy transfer process can be ignored. Secondly, *if* whatever changes in solvent that cause $\bar{C}_P$ (solv) to change also affect the enthalpies in the chemical reaction, changes in $\bar{C}_P$ (solv) may parallel changes in $\Delta H^{\ddagger}$ or ΔH. Similar logic holds for entropy terms. Figures 2 and 3 show changes in $\Delta H^{\ddagger}$, ΔH, $\Delta S^{\ddagger}$, and ΔS as a function of H_2SO_4 molarity. Clearly, changes in Figures 2 and 3 do not always parallel changes shown in Figure 1. The conclusion reached, then, is that changes in entropy and enthalpy of 1,3-cycloalkadiene hydration are explanable in terms of medium effects on enthalpy and entropy reaction coordinates. That is, the foregoing discussion justifies the assumption that changes in thermodynamic parameters observed do *not* reflect changes within the solvent alone. This allows discussion of not just the free energy changes, as is customary in acidity function treatments (activity coefficient ratio changes, etc.), but of the relative contribution of enthalpy and entropy to the overall smooth change in free energy (reflected as a smooth increase in f_D/f_{tr^+} and f_D/f_{ROH} terms).

Activation Parameters. Clearly, the medium dependence of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ does not parallel changes in comparable solvent thermodynamic properties (cf. Figures 1 and 2). Both $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ *decrease* up to 6 M H_2SO_4. A plot of $\Delta H^{\ddagger}$ vs. $\Delta S^{\ddagger}$ is linear through 5.6 M H_2SO_4 with a slope (β)[33] of 670, indicating that changes in $\Delta H^{\ddagger}$ predominate over compensating changes in $\Delta S^{\ddagger}$. Beyond 5.6 M H_2SO_4 the data show some scatter but a new line appears to be established of slope 80, indicating that changes in $\Delta S^{\ddagger}$ predominate over compensating changes in $\Delta H^{\ddagger}$. Thus the rather smooth change in free energy observed (as reflected in continuously increasing f_D/f_{tr^+} ratios, for example) is attributed to enthalpy decrease up to 5.6 M H_2SO_4 and entropy increase beyond 5.6 M H_2SO_4. Further, the linear relationship of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ suggests a common source of medium dependence. In moderately concentrated acid solution (5.6–10.3 M) the increasing entropy of activation is qualitatively consistent with Scheme I: an H_3O^+ species is formally bonded to the substrate in the transition state, the increasing entropy arises from the less strongly solvated tr^+ relative to H_3O^+ (the H_2O:H_2SO_4 molar ratio changes from 7.5:1 to 2.9:1 over this region).[4] The slight increase in $\Delta H^{\ddagger}$ is scarcely outside experimental error over this range.

Rationalization of changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ in dilute acid (0.5–5.6 M) is more complex, but still consistent with Scheme I. The increase in f_D/f_{tr^+} ratio was explained in terms of solvation requirement for tr^+ being intermediate to that of triaryl carbinols and anilinium ions: that is reflected in an overall *decrease* in $\Delta G^{\ddagger}$ over this acid range. Water is present in excess over this range of acidity ([H_2O]:[H_2SO_4] changes from 55:1 to 7.5:1):[4] decreasing $\Delta S^{\ddagger}$ reflects incorporation of the solvent aggregates in the transition state, an effect which appears to be rather dramatically overcome by increasing solvent structure above 5.6 M H_2SO_4. The 9 kcal/mol decrease in $\Delta H^{\ddagger}$ over the dilute acid range is consistent with a dielectric effect (a greater "salting-in" of tr^+ than reactants). However as water becomes less capable of solvating tr^+, the dielectric effect is compensated for by loss of solvating ability and $\Delta H^{\ddagger}$ appears nearly medium independent beyond 5.6 M H_2SO_4. The common source of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ changes, then, is capability of water to solvate ions in solution. In this regard it is striking that the minima in the curves of Figure 2 occur at H_2O:H_2SO_4 molar ratio of 7:1. Assuming that three water molecules are needed to solvate the three partially negative oxygens of HSO_4^- and four water molecules are needed to solvate the three partially positive protons of H_3O^+, the total requirement is 7:1 = [H_2O]:[H_2SO_4].

Medium dependence of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ suggest that the availability of water as solvating agent controls changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. Further, these quantities do not change continuously over normal acidity ranges studied but seem to be quite sensitive to solvent structure, as determined by existence of "free water" (water molecules not specifically solvating a δ^+ H–O or a δ^- O–S).

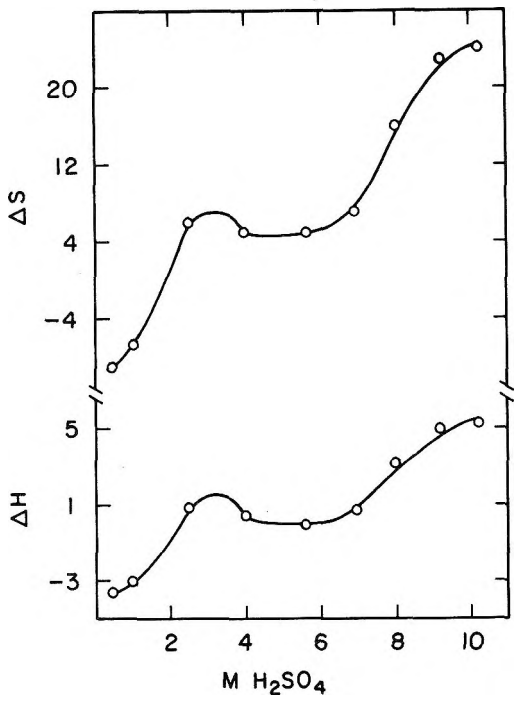


Figure 3. Plot of entropy (ΔS, cal/deg mol, top portion) and enthalpy (ΔH, kcal/mol, bottom portion) calculated from the equilibrium ratio vs. molarity of sulfuric acid in water. Smooth curve represents data in Table II, considering error limits and normalizing ΔH and ΔS for 1,3-cyclooctadiene to scale for 1,3-cyclohexadiene (e.g., ΔH plotted $\geq$5.6 M H_2SO_4 = ΔH (1,3-cyclooctadiene) − 3.5 kcal mol^{-1}. The amount 3.5 kcal mol^{-1} is the difference between the ΔH values for the two compounds at the common acid molarity 5.64 M H_2SO_4).

Equilibrium Thermodynamic Parameters. Medium dependence of ΔH and ΔS parallels changes in $\bar{C}_P$ (solv), as evident from Figures 1 and 3. A plot of ΔH vs. ΔS is linear and the slope is 265; that is, changes in ΔH are almost compensated for by changes in ΔS and the overall ΔG is nearly constant (which is reflected by the very small change in log (equil ratio) in Table III). It is striking that the curves in Figures 1–3 exhibit minima at about 6 M H_2SO_4 ($[H_2O]$:$[H_2SO_4]$ $\simeq$ 7:1). Further, the linearity of ΔH and ΔS over the entire acidity range suggests that changes in ΔH, ΔS, and $\bar{C}_P$ (solv) with acidity have a common source over the range. It is possible, of course, that the changes in ΔH and ΔS are fortuitously similar to changes in $\bar{C}_P$ (solv): the former may change because of significant protonation of 2-cycloalkenols above 4–5 M H_2SO_4. We prefer to link ΔH, ΔS, and $\bar{C}_P$ (solv), but available data do not justify any conclusions. In other words, there are sufficient open parameters to explain *any* medium dependence in Figure 3. Therefore we merely report the above observations with the comment that sulfuric acid solutions, based on these thermodynamic properties, seem to undergo a definite sort of solvent change at ~6 M H_2SO_4.

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Registry No.—H_2SO_4, 7664-93-9; 1,3-cyclohexadiene, 592-57-4; 1,3-cyclooctadiene, 1700-10-3.

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Aromatic Substitution of Olefins. 25.[1] Reactivity of Benzene, Naphthalene, Ferrocene, and Furan toward Styrene, and the Substituent Effect on the Reaction of Monosubstituted Benzenes with Styrene

Yuzo Fujiwara,* Ryuzo Asano, Ichiro Moritani, and Shiichiro Teranishi

Department of Chemistry, Faculty of Engineering Science, Osaka University, Machikaneyama, Toyonaka, Osaka 560, Japan

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The relative reactivity of various aromatic compounds toward styrene in the presence of palladium(II) acetate has been examined by competitive reactions. The order of reactivity is benzene < naphthalene < ferrocene < furan. This result and the effect of substituents on the reactions of monosubstituted benzenes with the olefin are similar to those of electrophilic aromatic substitution, which suggests that the present reaction involves an electrophilic attack of Pd^{II} on the aromatic ring to form an aromatic palladium σ complex.

In 1967 we reported a novel class of reactions wherein the double bond of olefins undergoes substitution reactions with aromatic compounds in the presence of palladium(II) salts, and opened a new area of the palladium-promoted reactions between aromatic compounds and olefins.[2]

Heck reported the related arylation reaction of olefins with arylating agents such as arylmercuric halides in the presence of group 8 metal salts, especially those of palladium.[3] Most recently, Heck et al. also described that aryl halides could react as an arylating agent.[4] In our reaction, the aromatic compound itself reacts with the olefin. It has been found that benzenoid as well as nonbenzenoid aromatic compounds undergo this reaction.[5]

Although the addition–elimination mechanism has been proposed for this type of reaction,[3] the nature of the first step, forming an aryl–palladium σ complex, is not yet fully understood. To help to clarify this point, we have investigated the reactivity of the various aromatic compounds, and the substituent effect on the reactivity of monosubstituted benzenes in the aromatic substitution reaction occurring between aromatic compounds and olefins.[6]

The reactivities of benzene, naphthalene, ferrocene, and furan toward styrene and the substituent effect on the reactions of monosubstituted benzenes with the olefin are similar to those of the electrophilic aromatic substitution. Hence we conclude that this reaction involves electrophilic aromatic substitution as the first step to form an aromatic Pd σ complex, followed by its addition to the olefin and elimination of a Pd–H unit.

Results

Reactivity of Benzene, Naphthalene, Ferrocene, and Furan toward Styrene. The reactivity was investigated by competitive reaction using styrene, which is most reactive, as the standard olefin and equimolar amounts of the aromatic substrates. The results are summarized in Table I.

From the reaction of benzene and naphthalene, *trans*-2-styrylnaphthalene[7] (**2**) and *trans*-stilbene (**1**) were obtained in 20 and 5% yields, respectively, together with a 11% yield of *trans,trans*-1,4-diphenylbutadiene (**3**).[9]

From the competitive reaction of naphthalene and ferrocene toward styrene, we obtained a 19% yield of *trans*-styrylferrocene (**4**) and a trace amount of **2** with 8% yield of **3**.

Ferrocene and furan led to *trans*-2-styrylfuran (**5**) and *trans,trans*-2,5-distyrylfuran (**6**) in 15 and 40% yields,[10] respectively, and no product derived from ferrocene was detected indicating that furan is far more reactive than ferrocene.

From these results, we estimate the order of reactivity as benzene (1) < naphthalene (4) < ferrocene (100) < furan (1000).[11] The sequence of reactivity is similar to but its magnitude is greatly different from that of the usual electrophilic aromatic substitution.

Table I. Competitive Reaction of Benzene, Naphthalene, Ferrocene, and Furan toward Styrene in the Presence of Palladium Acetate

Aromatic compd	Product and yield,[a] %
Benzene vs. naphthalene[b]	**1**, 5; **2**, 20
Naphthalene vs. ferrocene[c]	**4**, 19; **2**, trace
Ferrocene vs. furan	**5**, 15; **6**, 40

[a] Yields are based on styrene. [b] An 11% yield of **3** was also formed. [c] An 8% yield of **3** was also formed.

Table II. Reaction of Monosubstituted Benzenes with Styrene in the Presence of Palladium Acetate

Monosubstituted benzene	*trans*-Stilbene	Yield, %[d]
Toluene	*o*-Methylstilbene	17
	m-Methylstilbene	24
	p-Methylstilbene	33
Ethylbenzene[a]	*o*-Ethylstilbene	11
	m-Ethylstilbene	23
	p-Ethylstilbene	48
Anisole	o-Methoxystilbene	30
	m-Methoxystilbene	5
	p-Methoxystilbene	48
Chlorobenzene[b]	*o*-Chlorostilbene	10
	m-Chlorostilbene	22
	p-Chlorostilbene	32
Nitrobenzene[c]	o-Nitrostilbene	4
	m-Nitrostilbene	29
	p-Nitrostilbene	4

[a] Trace amounts of **3** and β-acetoxystyrene were also formed. [b] A 3% yield of **3** was also formed. [c] A 7% yield of **3** was also formed. [d] Yields are based on styrene utilized.

Reactions of Monosubstituted Benzenes with Styrene. On the reactions of monosubstituted benzenes with olefins, we briefly reported that the position of the substitution is controlled by the ortho-para directing nature of the alkyl group, and by the meta-directing nature of the nitro group.[12] In connection with the study described above, we have reexamined the reactions of monosubstituted benzenes with styrene using gas chromatography equipped with FID since the earlier work was done using column chromatography for analysis of the products. Mixtures of palladium(II) acetate, styrene in equivalent amounts, acetic acid, and an excess of the monosubstituted benzenes were stirred for 8 h at 110 °C. The results are summarized in Table II. It was revealed that

Table III. Competitive Reaction of Benzene and Monosubstituted Benzenes toward Styrene in the Presence of Palladium Acetate

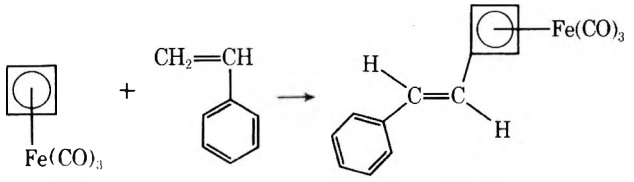
Monosubstituted benzene	Product[a] *trans*-Stilbene, % yield	Trans-monosubstituted stilbene	% yield
		o-Methylstilbene	11.6
Toluene	24.4	*m*-Methylstilbene	15.3
		p-Methylstilbene	21.6
		o-Ethylstilbene	6.1
Ethylbenzene	26.3	*m*-Ethylstilbene	12.2
		p-Ethylstilbene	18.2
		o-Methoxystilbene	26.0
Anisole	13.8	*m*-Methoxystilbene	3.8
		p-Methoxystilbene	41.5
		o-Chlorostilbene	4.1
Chlorobenzene	42.2	*m*-Chlorostilbene	10.5
		p-Chlorostilbene	15.0
		o-Nitrostilbene	0.5
Nitrobenzene	23.9	*m*-Nitrostilbene	5.2
		p-Nitrostilbene	0.5

[a] Yields are based on styrene used.

in the cases of CH_3, C_2H_5, and Cl groups, considerable amounts of the meta-substituted stilbenes were also formed and no remarkable ortho-para directing nature of the groups was observed. However, OCH_3, a strong electron-releasing group, and NO_2, a strong electron-withdrawing group, have a tendency to show the ortho-para and meta orientation, respectively.

In order to clarify the reactivity of the monosubstituted benzenes, competitive reactions with benzene as a standard were carried out. The results, summarized in Table III, again show general trends similar to the case of the electrophilic aromatic substitution.

Since it became apparent that this reaction is an electrophilic aromatic substitution, it was expected that cyclobutadiene–metal complexes should also react with olefins. Reaction of tricarbonyl(η-cyclobutadiene)iron(0) with styrene and $Pd(OAc)_2$ in a mixture of dioxane and acetic acid under reflux for 8 h gave a 6% yield of light yellow oil, tricarbonyl(η-*trans*-styrylcyclobutadiene)iron(0) (**7**).



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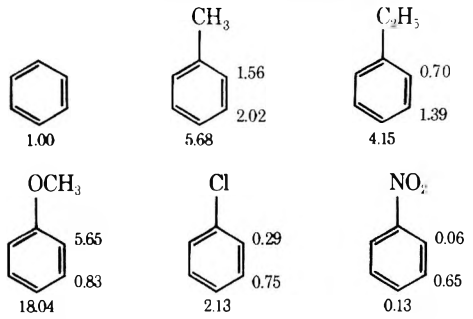
Discussion

From the data in Table III, we have calculated the partial rate factors as shown in Chart I.[13] It is of interest that both direction of substitution and the reactivity are not so strongly influenced by the substitution on a benzene ring as in the usual electrophilic aromatic substitution. With respect to orientation, OCH_3 and NO_2 groups direct ortho-para and meta, respectively. The electron-releasing groups increase the reactivity, but the difference in the reactivity is very small compared to the usual aromatic substitution. For example, in the nitration of monosubstituted benzenes, toluene is 10^6 times as reactive as nitrobenzene[14] but in the present reaction, the relative rate of anisole and nitrobenzene is only 20:1.

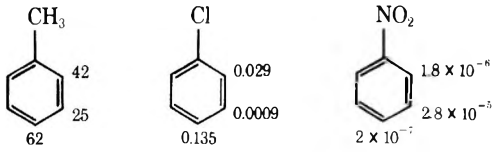
In Figure 1, the Hammett plots of the logarithm of the partial rate factors and σ^+ are shown. With respect to the para position, a good straight line was obtained and one can see a tendency characteristic of the electrophilic aromatic substitution. It is noted that the absolute value of ρ (-1.4) is somewhat smaller than that of the usual aromatic substitution. For example, ρ values for bromination, chlorination, and Friedel–Crafts ethylation of monosubstituted benzenes are reported to be -12.1,[15] -8.1,[16] and -2.4,[17] respectively. Although the small absolute ρ value seems to suggest a radical process, this possibility might be ruled out by the following facts: (1) Pd^{II} is a diamagnetic species, (2) radical inhibitors such as benzoquinone, *tert*-butylcatechol, or oxygen did not have a predictable effect on the reaction, (3) no evidence was obtained that ortho substitution is favored over meta and para substitution, which is typical of the radical process,[18] (4) anisole is about 20 times as reactive as nitrobenzene, and both nitrobenzene and chlorobenzene are less reactive than benzene itself despite the fact that substituents on a benzene ring increase the substitution rate in the radical aromatic substitution,[18] (5) no by-products typical of the radical process were obtained.

These observed substituent effects and the similarity in the reactivity of various aromatic compounds show that the reaction represents an electrophilic aromatic substitution, and that the reaction would proceed via electrophilic attack of Pd^{II} to a benzene ring forming an aryl–palladium σ complex.

Chart I. Partial Rate Factors in the Substitutions of Monosubstituted Benzenes with Styrene in the Presence of Palladium Acetate



cf. partial rate factors in nitration of some monosubstituted benzenes[a]



[a] J. D. Roberts and H. C. Caserio, "Basic Principles of Organic Chemistry", W. A. Benjamin, New York, N.Y., 1964, p 800.

Experimental Section

All melting points are uncorrected. Infrared spectra were recorded by a Japan Spectroscopic IR-E spectrometer. The NMR spectra were obtained by a Japan Electron Optics JNM-4H-100 or JEOL C-60 HL spectrometer using Me_4Si as an internal standard.

Materials. Palladium acetate was prepared according to the procedure of Wilkinson and co-workers.[21] Benzene, toluene, ethylbenzene, and anisole were refluxed with sodium metal and distilled. Nitrobenzene and chlorobenzene were dried over anhydrous calcium chloride and distilled. Acetic acid was dried over phosphorus pentoxide for 1 week and distilled through a 45-cm Widmer distilling column. Styrene was dried over sodium sulfate and distilled under reduced pressure.

General Procedure for Competitive Reaction of Aromatic Compounds. Mixtures of palladium acetate (10 mmol), styrene in equivalent amount, two aromatic compounds (10 mmol each), dioxane (120 ml), and acetic acid (30 ml) were stirred for 8 h at reflux. The resulting mixture was treated as reported already[2] and the products were analyzed and isolated by GLC or column chromatography. Identities with the products formed were proven by mixture melting point, ir, or NMR comparison with authentic samples. The melting points of the styryl derivatives are listed in the following section.

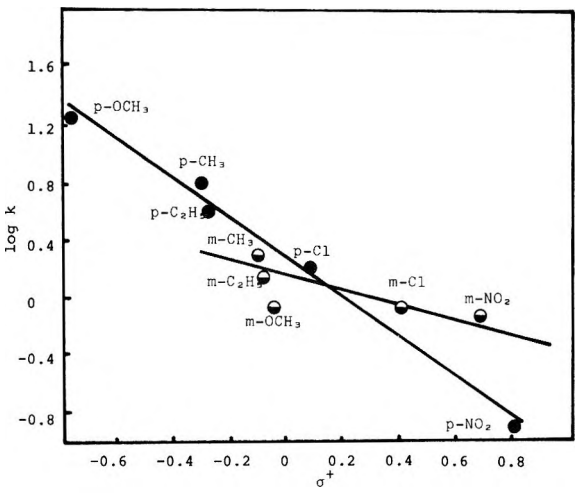


Figure 1. Plots of the logarithm of the partial rate factors k vs. σ^+ for substitution of para- (●) and meta- (◒) substituted benzenes with styrene in the presence of palladium acetate.

Styryl-Substituted Aromatic Compounds. *trans*-2-Styrylnaphthalene (**2**), mp 143 °C,[22] *trans*-styrylferrocene (**4**), mp 119–119.5 °C,[23] *trans*-2-styrylfuran (**5**), mp 52.5–54 °C,[24] *trans,trans*-2,5-distyrylfuran (**6**), mp 144–145.5 °C.[24]

General Procedure for Reaction of Monosubstituted Benzenes with Styrene. Mixtures of palladium acetate (6 mmol), styrene (6 mmol), monosubstituted benzene (60 ml), and acetic acid (14 ml) were stirred for 8 h at 110 °C. The resulting mixture was treated as described already[2] and the products were analyzed and isolated by GLC and column chromatography. The products were identified by the same procedure described above. Properties of stilbenes have been reported.[2]

General Procedure for Competitive Reaction of Styrene with Monosubstituted Benzenes. Mixtures of styrene (6 mmol), palladium acetate (6 mmol), benzene (400 mmol), monosubstituted benzene (400 mmol), and acetic acid (15 ml) were stirred at 90 °C for 8 h. The products were analyzed by GLC. The results are listed in Table III.

Reaction of Tricarbonyl(η-cyclobutadiene)iron(0) with Styrene. A solution of tricarbonyl(η-cyclobutadiene)iron(0) (10 mmol),[25] styrene (10 mmol), and palladium acetate (20 mmol) in a mixture of dioxane (160 ml) and acetic acid (40 ml) was refluxed for 8 h. After workup, the residue was chromatographed on a column of alumina. Elution with petroleum ether gave the starting cyclobutadiene complex and the subsequent elution gave a light yellow oil. This was assigned to be tricarbonyl(η-*trans*-styrylcyclobutadiene)iron(0) (**7**),[8] 6% yield: ir (Nujol) 2080, 1970, 960, 934, 831, 759, and 701 cm^{-1}; NMR (CCl_4) τ 2.81 (m, 5 H), 3.55 (d, J = 16 Hz, 1 H), 3.85 (d, J = 16 Hz, 1 H), 5.73 (s, 2 H), and 5.96 (s, 1 H). Further elution with ether gave **3** in 16% yield. Finally elution with MeOH gave a tarry substance.

Registry No.—**2**, 2840-89-3; **4**, 1272-54-4; **5**, 21676-00-6; **6**, 41082-14-8; **7**, 58117-30-9; benzene, 71-43-2; naphthalene, 91-20-3; ferrocene, 102-54-5; furan, 110-00-9; toluene, 108-88-3; ethylbenzene, 100-41-4; anisole, 100-66-3; chlorobenzene, 108-90-7; nitrobenzene, 98-95-3; tricarbonyl(η-cyclobutadiene)iron(0), 12078-17-0; styrene, 100-42-8.

References and Notes

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Additional Evidence of a New Type of Anchimeric Assistance in Quaternization Reactions of Phosphines and Arsines

William E. McEwen,* James E. Fountaine, Donald N. Schulz, and Wen-I Shiau

Department of Chemistry, The University of Massachusetts, Amherst, Massachusetts 01002

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Rate data for the reactions of aryldiethylphosphines with ethyl iodide in acetone solution, of triarylphosphines with benzyl chloride in benzene–methanol (3:2) solution, and of triarylarsines with benzyl bromide in chloroform solution are presented. A comparison with literature data reveals that rate and activation parameter profiles are distinctly different for anisyldialkylphosphines and anisyldialkylamines in reactions with alkyl halides, and this supports the concept of an important contribution to the stabilization of the transition state caused by overlap of a pair of 2p electrons of the oxygen of an ortho methoxy group with an empty 3d (or hybrid) orbital of phosphorus. A similar effect shows up in the NMR spectra of the quaternary phosphonium salts. The effects of substituents other than methoxy in the reactions of triarylphosphines with benzyl chloride have been evaluated in terms of the geometry of the transition state, the HSAB principle, and ordinary substituent and steric effects. The fact that the presence of a ferrocenyl group has a larger effect in the retardation of the rate of alkaline cleavage of a ferrocenylphosphonium salt than it does in the acceleration of the rate of displacement of a ferrocenylphosphine on an alkyl halide provides additional evidence that the transition state for the latter type of reaction lies closer to the reagents than to the products along the reaction coordinate of the energy profile diagram. The greater degree of anchimeric assistance observed in the reactions of *o*-anisylarsines with alkyl halides than in the reactions of *o*-anisylphosphines with alkyl halides, even though the latter reactions are fundamentally much faster, is interpreted in terms of the principle that increasing electron demand results in increasing electron supply when an anchimeric assistance effect is operative. NMR spectral data and equilibrium considerations are also discussed with respect to the quaternary arsonium salts formed in the alkylation reactions.

Rate data for the quaternization reactions of various triarylphosphines with benzyl chloride, benzyl bromide, and *n*-butyl chloride have been presented in previous papers.[1,2] Two particularly striking effects were noted. (1) The presence of an *o*-methoxy group in the phosphine causes a marked acceleration of the reaction. (2) The ratio of the rates of reaction of a given triarylphosphine with benzyl chloride and *n*-butyl chloride is less than 20, probably the smallest such ratio ever found in SN2 reactions of these halides. An explanation of these effects was offered based partly on the concept of overlap of a pair of 2p electrons of an *o*-anisyl group with a 3d orbital (or hybrid orbital) of phosphorus in the transition state and partly on the concept that the transition state for each of the reactions lies much closer to the reagents than to the products along the reaction coordinate of the energy profile diagram. We now wish to present new data with respect to substituent and structural effects and to evaluate these data in terms of the concepts cited above.

Since triarylamines (including tris-*o*-anisylamine) do not undergo quaternization reactions with *n*-butyl chloride, benzyl chloride, and benzyl bromide (at least under the reaction conditions employed in our previous[1,2] kinetics studies), we were unable in our previous papers to make a direct comparison between the phosphorus and nitrogen systems. (It would be anticipated that the postulated 2p–3d overlap would not occur in the amine reactions.) Therefore, we have now carried out kinetics studies of the reactions of selected aryldiethylphosphines with ethyl iodide in acetone solution. We selected this system for two reasons. (1) Henderson and Buckler[3] have developed a convenient procedure for studying the kinetics of the reaction of the parent phosphine, phenyldiethylphosphine, with ethyl iodide, and they consider this to be a "normal" system, based on several criteria (correlation of data by means of the Taft–Hammett equation, a reasonable reactivity–solvent polarity profile, etc.). (2) Evans, Watson, and Williams[4] have reported rate data for the reactions of dialkylanilines with alkyl halides which can be used for purposes of comparison. Our data for the reactions of aryldiethylphosphines with ethyl iodide in acetone solution are presented in Table I. It is clear that the new data on the phosphine reactions parallel the results presented previously.[1,2] The relative rates of reaction of *o*-anisyldiethylphosphine, *p*-anisyldiethylphosphine, phenyldiethylphosphine, and *m*-anisyldiethylphosphine with ethyl iodide in acetone solution at 35.0 °C are 6.96, 1.76, 1.00, and 0.91, respectively. By way of contrast, the relative rates of reaction of *o*-methoxydimethylaniline, *p*-methoxydimethylaniline, and dimethylaniline with methyl iodide in methanol solution at 35.0 °C are 1.88, 4.37, and 1.00, respectively.[4] These differences in reactivity profiles are readily explained in terms of overlap of the 2p electrons of the *o*-methoxy group with an empty 3d orbital (or hybrid orbital) of phosphorus in the transition state of the reaction of *o*-anisyldiethylphosphine with ethyl iodide, whereas there is no readily available d orbital in the nitrogen system to provide similar stabilization of the transition state.

Chock and Halpern[5] have suggested that a highly polar transition state, one closely resembling the product, is formed in the "oxidative addition" of iridium phosphine complexes of the type *trans*-$[IrCl(CO)(PMe_2Ar)_2]$ with methyl iodide. Therefore, the degree of anchimeric assistance provided by an *o*-anisyl group in this system should be much larger than that in our system, the transition state of which is presumed to lie close to the reagents along the reaction coordinate of the energy profile diagram. The data of Miller and Shaw[6] illustrate this point nicely, the *o*-anisyl complex being 78 times more reactive than the *p*-anisyl complex. The presumed transition state for the reaction of the *o*-anisyl complex with methyl iodide is shown in Figure 1.

We speculated in our previous paper[1] that the transition state for the reaction of an *o*-anisylphosphine with an alkyl halide might be of the type depicted in Figure 2. As an additional test of this hypothesis, we have now investigated the effects of other substituents on the reactions of triarylphosphines with benzyl chloride in benzene–methanol (3:2) solution. The results are summarized in Table II.

The effects of a methyl substituent are unexceptional. A methyl group in the para position is mildly electron donating by an inductive effect. This causes a small increase in the nucleophilicity of the phosphine and consequently a small increase in the rate of reaction. A methyl group in the ortho position obviously cannot enter into any kind of a direct bonding interaction with phosphorus in the transition state. The fact that the relative rate of the *o*-tolyl compound is but

Table I. Rate Data for Reactions of Aryldiethylphosphines with Ethyl Iodide in Acetone Solution

Registry no.	Phosphine	Temp, °C[a]	k_2, l. mol^{-1} h^{-1} [b]	E_a	$\Delta S^{\ddagger}$ (35.0 °C)
1605-53-4	Diethylphenyl	25.0	0.83 ±0.00		
		35.0	1.81 ±0.00	13.5	−31.8
		45.0	3.43 ±0.00		
58325-38-5	*o*-Anisyldiethyl	25.0	5.82 ±0.25		
		35.0	12.60 ±0.25	14.0	−26.2
		45.0	25.70 ±0.35		
58325-39-6	*m*-Anisyldiethyl	25.0	0.82 ±0.01		
		35.0	1.65 ±0.06	13.0	−33.6
		45.0	3.34 ±0.03		
17310-20-2	*p*-Anisyldiethyl	25.0	1.51 ±0.01		
		35.0	3.19 ±0.03	13.3	−31.2
		45.0	5.96 ±0.10		

[a] Maintained at ±0.1 °C. [b] Average deviation based on at least four experimental results.

Table II. Rate Constants for Reactions of Triarylphosphines with Benzyl Chloride in Benzene–Methanol (3:2) at 31.0 ± 0.1 °C

Registry no.	Phosphine	$k_2 \times 10^2$, l. mol^{-1} h^{-1} [a]	Rel rate
603-35-0	Triphenyl	7.22[8] ± 0.13	1.00
5931-53-3	*o*-Tolyldiphenyl	2.17 ± 0.08	0.30
1031-93-2	*p*-Tolyldiphenyl	9.44 ± 0.26	1.31
13175-76-3	*o*-(Methoxymethyl)phenyldiphenyl	2.50 ± 0.16	0.35
35542-35-9	*p*-(Methoxymethyl)phenyldiphenyl	6.50 ± 0.19	0.90
14791-94-7	*o*-Thiomethoxyphenyldiphenyl	8.32 ± 0.37	1.15
35542-36-0	*p*-Thiomethoxyphenyldiphenyl	8.66 ± 0.25	1.20
35612-21-6	*o*-(Thiomethoxymethyl)phenyldiphenyl	2.04 ± 0.13	0.28
12098-17-8	Ferrocenyldiphenyl	20.1 ± 1.4	2.78
12278-69-2	Diferrocenylphenyl	24.1 ± 0.7	3.34

[a] Average deviation based on four experimental results.

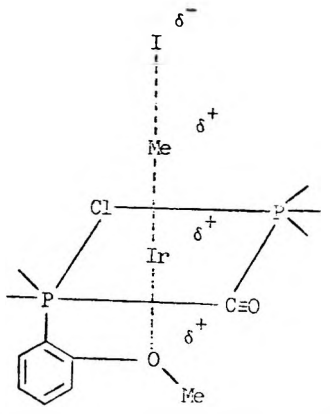

Figure 1. Proposed transition state for the reaction of *trans*-[IrCl(CO)(o-anisylPMe$_2$)$_2$] with methyl iodide.

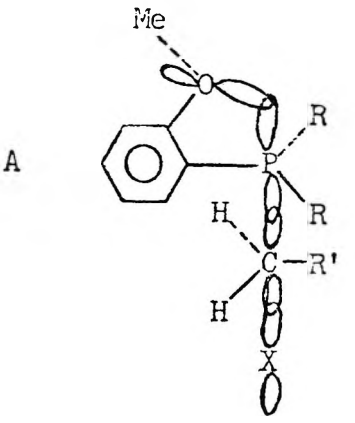

Figure 2. A possible transition state for the reaction of an *o*-anisylphosphine with an alkyl halide. Other geometries which would permit 2p–3d overlap are also conceivable.

0.30 indicates that an unfavorable steric compression in the transition state has a larger influence than the small, favorable inductive effect of the substituent.

The effect of a methoxy substituent has been discussed in detail previously.[1] The fact that the presence of an *o*-methoxymethyl substituent causes a decrease in the relative rate (0.35) can be understood in terms of the transition state depicted in Figure 2. The spatial requirements of the extra methylene group forces ring A down and to the right (in terms of Figure 2) so that it crowds the methylene group of R′CH$_2$X and also causes more interference between R and R′ groups. Thus, this unfavorable steric effect in the transition state becomes more important than the otherwise favorable 2p–3d overlap effect, and the relative rate of reaction is lowered. The observation that the presence of a *p*-methoxymethyl group causes the relative rate to be slightly less than 1.00 reflects the fact that the methoxymethyl substituent is mildly electron withdrawing in nature, thus decreasing slightly the nucleophilicity of the phosphine.

The HSAB principle[7] can be invoked to explain why the presence of an *o*-MeS group has less ability to promote the rate of reaction than the presence of an *o*-MeO group. The phosphorus atom of the developing phosphonium cation is a hard acid center, and therefore overlap is more effective with the hard base center, OMe, than with the relatively soft base center, SMe. Thus, the relative rate for the *o*-methoxy system is 7.42,[1,2] while that for the *o*-thiomethoxy system is but 1.15. Also, the relatively large size of the o-SMe group probably causes the same unfavorable steric effect in the transition state as described previously for the *o*-methoxymethyl system, but to a smaller degree. The *p*-SMe group is mildly electron donating, and its presence therefore causes the relative rate of

Table III. NMR Absorption Data Taken in $CDCl_3$ Solution for the Hydrogen Atoms of the Methylene Group Directly Bonded to Phosphorus in the Phosphonium Salts

Registry no.	Phosphonium cation	Anion	δ, ppm, CH_2	J_{PH}, Hz
1100-88-5	Triphenylbenzyl	Cl^-	5.42, d	15
14479-51-7	*o*-Tolyldiphenylbenzyl	Cl^-	5.32, d	15
13432-86-5	*p*-Tolyldiphenylbenzyl	Cl^-	5.64, d	15
58325-40-9	*o*-Thiomethoxyphenyldiphenylbenzyl	Cl^-	5.68, d	15
58325-41-0	*p*-Thiomethoxyphenyldiphenylbenzyl	Cl^-	5.51, d	15
58325-42-1	*o*-(Methoxymethyl)phenyldiphenylbenzyl	Cl^-	5.58, d	15
58325-43-2	*p*-(Methoxymethyl)phenyldiphenylbenzyl	Cl^-	5.67, d	14.5
58325-44-3	o-(Thiomethoxymethyl)phenyldiphenylbenzyl	Cl^-	5.76, d	14.5
58384-30-8	Ferrocenyldiphenylbenzyl	Cl^-	5.02, d	14
3040-69-5	Phenyltriethyl	I^-	2.93, d of q	13
58325-45-4	*o*-Anisyltriethyl	I^-	2.82, d of q	13
58325-46-5	*m*-Anisyltriethyl	I^-	2.95, d of q	13
58325-47-6	*p*-Anisyltriethyl	I^-	2.87, d of q	13

its reaction system to be 1.20. The presence of an *o*-CH_2SMe group, which combines an unfavorable steric effect with a relatively unfavorable HSAB effect, causes the relative rate to drop to 0.28.

Another (although not mutually exclusive with the HSAB concept) explanation for the lower reactivity of the *o*-thiomethoxyphenylphosphine as against the o-methoxyphenylphosphine lies in the strength of the partial bond formed in the neighboring group interaction of the ortho substituent with the central phosphorus atom. The energy of the phosphorus–oxygen bond is substantially greater than that of the phosphorus–sulfur bond.[9]

As in the reactions described previously,[1,2] the $\Delta S^{\ddagger}$ values for the reactions of aryldiethylphosphines with ethyl iodide (see Table I) are of greater importance in determining the relative rates of reaction than are the E_a values. An explanation for this effect was offered in a previous paper[1] and need not be repeated here. Although Evans, Watson, and Williams[4] did not calculate values of $\Delta S^{\ddagger}$ for the reactions of the various dimethylanilines with methyl iodide in methanol solution, their data permit such calculations to be made. For the reaction of *o*-methoxydimethylaniline, E_a = 15.9 and $\Delta S^{\ddagger}$ = −25.5; for the *p*-methoxydimethylaniline reaction, E_a = 14.3 and $\Delta S^{\ddagger}$ = −29.0. In this series, it is significant that the greater rate of the *p*-methoxy compound is attributable to a lower value of E_a.

The rate acceleration caused by the presence of a ferrocenyl group is relatively small. As shown in Table II, the relative rate of reaction of ferrocenyldiphenylphosphine with benzyl chloride is 2.78, while that of diferrocenylphenylphosphine is 3.34. On the other hand, the relative rates of reaction of benzyltriphenylphosphonium iodide, benzylferrocenyldiphenylphosphonium iodide, and benzyldiferrocenylphenylphosphonium iodide with sodium hydroxide in dimethoxyethane–water (1:1) at 62.2 °C are 163, 2.75, and 1.00, respectively.[10] These results support the concept that the transition state for the SN2 reaction of a tertiary phosphine with an alkyl halide lies closer to the reagents than to the products in the energy profile diagram. Thus, overlap of the ha_g molecular orbital[11] of a ferrocenyl group with a 3d (or hybrid) orbital of phosphorus in the transition state is relatively slight. However, in the phosphonium salts, a significant degree of overlap between the filled molecular orbital of the ferrocenyl group with an empty 3d orbital of phosphorus exists, and this results in a significant degree of stabilization of a ferrocenylphosphonium ion, as is also true with α-ferrocenylcarbonium ions.[12-17] Therefore, the phosphorus atom of the ferrocenylphosphonium ion is relatively resistant to attack by the hydroxide ion (cf. our earlier papers[18,19] for the detailed mechanism of phosphonium hydroxide decomposition), and this accounts for the marked decrease in rate when a ferrocenyl group is one of the substituents bonded to the phosphorus atom. The fact that the presence of a second ferrocenyl group does not further affect to any marked extent the rate of either the SN2 reaction of a phosphine or the rate of attack of a hydroxide ion on a phosphonium cation is consistent with the type of interaction depicted in Figure 2, in which only one such group can engage in a direct overlap interaction.

Additional support for the concept of 2p–3d overlap can be gained by examination of the ^1H NMR spectra of the phosphonium salts formed in the SN2 reactions of the various phosphines with alkyl halides. For reasons cited in the previous paper,[1] the chemical shift of the methylene group directly bonded to phosphorus in the phosphonium salt represents a better probe of the overlap than the chemical shift of a substituent on an aryl group bonded to the phosphorus. An upfield shift of the methylene hydrogen atoms is expected when the electron density at phosphorus is increased owing to an overlap effect. This anticipated effect is visible only in the spectra of the phosphonium salts formed by reactions in which anchimeric assistance is in evidence, as shown by the data presented in Table III. Of course, the effects may also be attributable in part to magnetic anisotropy of the substituent groups, and therefore they may not represent clear proof of the postulated overlap.

Additional insight into the potential reactivity of triarylphosphines with alkyl halides can sometimes be obtained by examination of the ultraviolet spectra of the phosphines. Previously,[1] we reported that the uv spectrum of *o*-anisyldiphenylphosphine possesses an "extra" band at 284 nm, presumably attributable to intramolecular charge transfer absorption. This observation presaged the 2p–3d overlap in the transition states of its reactions with alkyl halides. No such extra value of λ_{max} has been found in the uv spectra of the *o*-tolyl-, *o*-methoxymethyl-, and *o*-thiomethoxymethyldiphenylphosphines, and this coincides with the absence of anchimeric assistance in their reactions with alkyl halides. On the other hand, the *o*-thiomethoxy compound does possess an extra uv absorption peak at 304.5 nm, which suggests that this group has the requisite geometry for p–d overlap. However, the rate data for the reaction of this compound with benzyl chloride (Table II) show but a small enhancement of SN2 reactivity. Apparently, the proper spatial arrangement is offset by the unfavorable HSAB effect (vide supra).

Our first observations of a new and unusual anchimeric assistance effect were made when we first studied the rates of the quaternization reactions of triarylarsines with benzyl bromide in chloroform solution.[20] The pertinent data are summarized in Table IV. For purposes of comparison, the specific rate constant for the reaction of triphenylphosphine with benzyl bromide at 31.0 °C is 803 × 10^{-2} l. mol^{-1} h^{-1}, as reported in the previous publication.[1] Thus, triphenylphos-

Table IV. Rate and Equilibrium Constants for Reactions of Triarylarsines with Benzyl Bromide in Chloroform Solution at 29.6 ± 0.1 °C

Registry no.	Arsine	$k_2 \times 10^2$, l. mol^{-1} h^{-1}	K_{eq}
603-32-7	Triphenyl	3.58 ± 0.02	70.5 ± 2.1
2896-10-8	Tris(*p*-tolyl)	15.5 ± 0.1	1.5 ± 0.1 × 10^4
2417-85-8	Tris(*o*-tolyl)	0.00[a]	
35569-46-1	Tris(*p*-anisyl)	22.2 ± 0.3	9.0 ± 0.6 × 10^5
21920-60-5	Tris(*o*-anisyl)[b]	319.5 ± 7.0	

[a] The reaction was too slow to permit measurement of the rate. A sensitive qualitative test[23] for the formation of benzyltris(*o*-tolyl)arsonium bromide was found to be faintly positive after 1 week of reaction. [b] The concentration of tris(*o*-anisyl)arsine at equilibrium is too small to be measured accurately; thus, no meaningful value of K_{eq} could be obtained. It is obviously distinctly larger than 9 × 10^5, the value reported for the tris(*p*-anisyl) reaction.

phine is approximately 220 times more reactive than triphenylarsine in the quaternization reaction, and this reflects the well-documented greater nucleophilicity of a phosphine as against a corresponding arsine.[21] Another important point of comparison is that tris(o-anisyl)phosphine is 1.59 times more reactive than triphenylphosphine toward benzyl bromide in chloroform solution at 31.0 °C.[1] From the data presented in Table IV, it is apparent that tris(*o*-anisyl)arsine is 89.3 times more reactive than triphenylarsine toward benzyl bromide in chloroform solution at 29.6 °C. Undoubtedly, one of the major influences here is based on a steric effect; there is more room for the nonparticipating methoxy groups about the larger arsenic atom. Another important effect is based on the principle that increasing electron demand results in increasing electron supply when an anchimeric assistance effect is operative.[22,23] We consider the results cited above to represent yet another substantial line of evidence in support of the postulated 2p–3d overlap in the transition states of the *o*-anisylphosphine–alkyl halide reactions and of 2p–4d overlap in the *o*-anisylarsine–alkyl halide reactions.

As anticipated on the basis of known electronic effects of the substituents, and also on the basis of analogy with the SN2 reactions of triarylphosphines with alkyl halides,[1,2] the presence of *p*-methyl and *p*-methoxy substituents on the arsine brought about a relatively small increase in the rate of reaction as against the triphenylarsine result. Also, on the basis of the obvious steric effect, the presence of *o*-methyl substituents caused the reaction to be too slow to permit measurement of the rate. Rate data for the reactions of tri-*p*-chlorophenylarsine and tri-*p*-bromophenylarsine with benzyl bromide could not be obtained. Nevertheless, some useful information about these reactions was obtained. When these arsines were mixed with benzyl bromide in chloroform, they gave a positive qualitative test[24] for the arsonium ion after the solutions had been allowed to stand for 1 week at room temperature. However, when these solutions were warmed to 50–55 °C for a few minutes and tested again for the presence of the arsonium cation, a negative result was obtained. A positive test again resulted when the solution had been allowed to stand at room temperature for 1 week. Evidence for reversal of quaternary salt formation has also been reported by a number of other workers.[25,26] Consequently, we have determined the equilibrium constants for several of the reactions of triarylarsines with benzyl bromide, and these are given in Table IV. The order of the K_{eq} values parallels that of the specific rate constants.

The rates of the reactions of tris(o-anisyl)arsine and tris(*p*-anisyl)arsine with benzyl bromide in chloroform solution were also measured at 25.0 and 35.0 °C. The values for the ortho isomer were 233.9 × 10^{-2} l. mol^{-1} h^{-1} (25.0 °C) and 446.3 × 10^{-2} l. mol^{-1} h^{-1} (35.0 °C). The values for the para isomer were 15.5 × 10^{-2} l. mol^{-1} h^{-1} (25.0 °C) and 29.59 × 10^{-2} l. mol^{-1} h^{-1} (35.0 °C). From these data we could calculate $\Delta H^{\ddagger}$ values of 11.8 and 11.7 kcal mol^{-1} for the reactions of the ortho and para compounds, respectively, and $\Delta S^{\ddagger}$ values of −35 and −41 eu, respectively. As in the tertiary phosphine–alkyl halide reactions, the value of $\Delta S^{\ddagger}$ controls the rate more than the value of $\Delta H^{\ddagger}$ (or E_a). The proposed 2p–4d interaction in the *o*-anisyl reaction decreases the need for external solvation, and this leads to a markedly less negative value of $\Delta S^{\ddagger}$ and a faster rate of reaction. A more complete explanation of this effect has been given in our previous publication.[1]

The chemical shift effect cited previously is also apparent in the NMR spectra of the arsonium salts. The δ values found for the methylene protons in deuteriochloroform solution are 5.38 for benzyltriphenylarsonium bromide, 5.22 for benzyltris(*p*-tolyl)arsonium bromide, 5.15 for benzyltris(*p*-anisyl)arsonium bromide, and 4.70 for benzyltris(o-anisyl)arsonium bromide. Again, the apparent increased electron density at arsenic in the *o*-anisyl salt, presumably caused by 2p–4d overlap, brings about a pronounced upfield shift in the absorption of the methylene protons.

Experimental Section

The general statements with regard to physical constants, spectral data, analyses, the preparation of triarylphosphines, and the procedures used in the kinetics studies are the same as those given in the previous paper.[1] The physical constants and spectral data for the tertiary phosphines are presented in Table V, and the properties of the quaternary phosphonium halides are given in Table VI.

Preparation of Triarylphosphines by the Grignard Reaction. The procedure in each case was essentially the same as that reported for the preparation of o-anisyldiphenylphosphine in the previous paper.[1]

Preparation of *o*-(Methoxymethyl)phenyldiphenylphosphine. To a stirred mixture of 182 ml of a 2.25 M (0.41 mol) solution of *n*-butyllithium in hexane (Alfa Inorganics) and 30 ml of anhydrous diethyl ether contained in a three-necked flask under argon at 0 °C was added a solution of 82.4 g (0.41 mol) of *o*-bromobenzyl methyl ether[35] in 175 ml of anhydrous diethyl ether over a 30-min period. After the mixture had been stirred for an additional 1 h, a solution of 90.6 g (0.41 mol) of chlorodiphenylphosphine in 90 ml of anhydrous diethyl ether was added over 30 min at 0 °C. The mixture was allowed to warm to room temperature, and then it was refluxed for 1 h. Hydrolysis at 0 °C with 5% hydrochloric acid followed, and the mixture was extracted with diethyl ether. The ether layer was washed with water until neutral to litmus paper and subsequently concentrated with the aid of a rotary evaporator. The residue was dissolved in acetone at room temperature and then refrigerated at −15 °C; *o*-(methoxymethyl)phenyldiphenylphosphine, mp 94.0–95.5 °C, crystallized from the acetone solution and weighed 50.9 g (41%).

Preparation of Other Triarylphosphines by Use of a Lithium Reagent. *p*-Bromobenzyl methyl ether was prepared by the method of Supniewski and Adams[36] and converted to *p*-(methoxymethyl)phenyldiphenylphosphine by essentially the same method as that described for the ortho isomer, with the exception that the product was purified by vacuum distillation. *o*-Bromobenzyl methyl sulfide was prepared by the method of Breslow, Garratt, Kaplan, and LaFollette[37] and converted to *o*-(thiomethoxymethyl)phenyldiphenylphosphine by the method described above.

Preparation of *m*-Anisyldichlorophosphine. To the Grignard reagent prepared in a 500-ml three-necked flask under nitrogen from 4.8 g (0.2 g-atom) of magnesium turnings, 30 ml of dry tetrahydrofuran, and a solution of 37.4 g (0.2 mol) of *m*-bromoanisole in 150 ml of dry tetrahydrofuran was added slowly a solution of 27.2 g (0.2 mol) of zinc chloride[38] in 180 ml of dry tetrahydrofuran at 0 to −5 °C, with stirring. The organozinc halide reagent was transferred under nitrogen to a 500-ml dropping funnel.

A solution of 50 ml (0.57 mol) of phosphorus trichloride in 100 ml of dry tetrahydrofuran was prepared in a 1000-ml three-necked flask, and the contents were kept in the vicinity of −20 °C.[39] The organozinc halide reagent was added slowly to the chilled solution under nitrogen with stirring. The reaction mixture was then refluxed for 4 h, cooled

Table V. Physical Constants and Spectral Data for Tertiary Phosphines

Phosphine	Reagents (solvent)	Mp or bp, °C	Reported mp or bp, °C	Cryst solvent (% yield)	NMR, δ ($CDCl_3$)
o-Tolyldiphenyl	o-TolylMgCl + Ph_2PCl (THF)	69–71	73[27]	MeOH (72)	3.74 s, 6.97–7.64 m
p-Tolyldiphenyl	p-TolylMgBr + Ph_2PCl (THF)	65.2–66.8	66.5[28]	EtOH (55)	2.28 s, 7.01–7.30 m
o-(Methoxymethyl)phenyldiphenyl	o-$MeOCH_2C_6H_4Li$ + Ph_2PCl (hexane–ether)	94.0–95.5[a]		Acetone (41)	3.22 s, 4.61 s, 6.78–7.30 m
p-(Methoxymethyl)phenyldiphenyl	p-$MeOCH_2C_6H_4Li$ + Ph_2PCl (hexane–ether)	157–160 (0.05 mm)		(40)	3.26 s, 4.30 s, 7.04–7.48 m
o-Thiomethoxyphenyldiphenyl	o-$MeSC_6H_4MgBr$ + Ph_2PCl (THF)	104.5–105.2	101–102[29]	EtOH (36)	2.46 s, 6.97–7.67 m
p-Thiomethoxyphenyldiphenyl	p-$MeSC_6H_4MgBr$ + Ph_2PCl (THF)	109.0–110.5[b]		MeOH (40)	2.44 s, 7.41–7.67 m
o-(Thiomethoxymethyl)phenyldiphenyl	o-$MeSCH_2C_6H_4Li$ + Ph_2PCl (hexane–ether)	155–163 (0.05 mm)[c]		(33)	1.86 s, 3.91 s, 6.87–7.41 m
Ferrocenyldiphenyl	Ferrocene + Ph_2PCl (heptane, $AlCl_3$)	122–124	122–124[30,31]	EtOH (45)	4.04–4.50 m, 7.15–7.60 m
Diferrocenylphenyl	Ferrocene + $PhPCl_2$ (heptane, $AlCl_3$)	193–195	191–193[30,31]	Benzene–heptane	3.8–4.3 m, 7.1–7.6 m
Diethylphenyl	EtMgBr + $PhPCl_2$ (ether)	69–70 (0.18 mm)	65–67 (1 mm)[32]	(54)	0.98 d of t (J_{P-CH} = 15 Hz), 1.64 q, 7.1–7.75 m
o-Anisyldiethyl	EtMgBr + o-$MeOC_6H_4PCl_2$ (ether)	107–108 (0.9 mm)		(85)	1.0 d of t (J_{P-CH} = 14.4 Hz), 1.66 q, 3.75 s, 6.65–7.50 m
m-Anisyldiethyl	EtMgBr + m-$MeOC_6H_4PCl_2$ (ether)	101–102 (1.3 mm)		(78)	1.0 d of t (J_{P-CH} = 15 Hz), 1.66 q, 3.72 s, 6.70–7.46 m
p-Anisyldiethyl	EtMgBr + p-$MeOC_6H_4PCl_2$ (ether)	92–93 (0.5 mm)	108 (1.5)[33]	(57)	0.97 d of t (J_{P-CH} = 15 Hz), 1.64 q, 3.72 s, 6.75–7.05 m, 7.25–7.65 m

[a] Anal. Calcd for $C_{20}H_{19}OP$: C, 78.41; H, 6.25; P, 10.11; O, 5.22. Found: C, 78.36; H, 6.16; P, 10.00; O, 5.20. [b] Anal. Calcd for $C_{19}H_{17}PS$: C, 74.00; H, 5.56; P, 10.05. Found: C, 73.89; H, 5.51; P, 10.15. [c] Anal. Calcd for $C_{20}H_{19}PS$: C, 74.51; H, 5.94; P, 9.61. Found: C, 74.86; H, 5.96; P, 9.49.

to room temperature, and filtered. The light yellow filtrate was distilled to remove the solvent. The remaining liquid was fractionated under reduced pressure. The product was obtained as a colorless liquid, 18.2 g (44%), bp 76–78 °C (0.5 mm).

The ^1H NMR spectrum of this compound in deuteriochloroform showed a singlet at δ 3.70 ppm (3 H) and a multiplet at δ 6.65–7.62 ppm (4 H).

Synthesis of *m*-Anisyldiethylphosphine. To the Grignard reagent prepared in a three-necked flask under nitrogen from 9.6 g (0.4 g-atom) of magnesium turnings, 110 ml of anhydrous diethyl ether, and a solution of 44 g (0.4 mol) of ethyl bromide in 150 ml of anhydrous diethyl ether was added dropwise a solution of 17.8 g (0.085 mol) of *m*-anisyldichlorophosphine in 40 ml of anhydrous diethyl ether at −10 to −15 °C with stirring over a period of 0.5 h. The reaction mixture was refluxed for 1 h. It was then hydrolyzed at 0 °C with 110 ml of saturated ammonium chloride solution, and additional water was added to dissolve a white solid which had formed. The ether layer was separated from the aqueous solution and dried over anhydrous magnesium sulfate. Removal of the solvent by simple distillation left a faint-colored liquid, which was fractionated under reduced pressure, bp 101–102 °C (1.3 mm). The yield of the colorless liquid was 13 g (78%).

The ^1H NMR spectrum of this compound in deuteriochloroform showed a doublet of triplets centered at δ 1.0 ppm (6 H, J_{P-CH} = 15 Hz), a quartet coupled with the phosphorus centered at δ 1.66 ppm (4 H), a singlet at δ 3.72 ppm (3 H), and a multiplet at δ 6.70–7.46 ppm (4 H).

Other Aryldiethylphosphines. These were prepared in essentially the same manner as that described for *m*-anisyldiethylphosphine. o-Anisyldichlorophosphine was obtained in 60% yield as a colorless liquid: bp 124.6–125.0 °C (1.2 mm) [lit.[40] 88.5–89.0 °C (0.52 mm)]; NMR ($CDCl_3$) δ 3.78 (s, 3 H) and 6.70–8.05 (m, 4 H). o-Anisyldiethylphosphine was obtained in 85% yield: bp 107–108 °C (0.9 mm); NMR ($CDCl_3$) δ 1.0 (d of t, 6 H, J_{P-CH} = 14.4 Hz), 1.66 (q, 4 H, J_{P-CH} = 14.4 Hz), 3.75 (s, 3 H), and 6.67–7.50 (m, 4 H). p-Anisyldichlorophosphine was obtained in 52% yield, bp 103–104 °C (0.23 mm) [reported 150 °C (13 mm),[41] 140 °C (10 mm)[33]]; NMR ($CDCl_3$) δ 3.72 (s, 3 H), 6.8–7.1 (m, 2 H), 7.6–8.0 (m, 2 H). p-Anisyldiethylphosphine was obtained in 57% yield: bp 92–93 °C (0.5 mm) [reported 166–171 °C (40 mm),[41] 108 °C (1.5 mm)[33]]; NMR ($CDCl_3$) δ 0.97 (d of t, 6 H, J_{P-CH} = 15 Hz), 1.64 (q, 4 H, J_{P-CH} = 15 Hz), 3.72 (s, 3 H), 6.75–7.05 (m, 2 H), 7.25–7.65 (m, 2 H).

Preparation of Benzyltriarylphosphonium Chlorides. The same procedure as described in the previous paper[1] was used to prepare these salts.

Preparation of Aryltriethylphosphonium Iodides. These salts were isolated directly from the reaction solutions of the kinetics experiments by evaporation of the solvent under nitrogen.

Kinetics Procedure for Quaternization Reactions of Triarylphosphines with Benzyl Chloride. The procedure was identical with that described previously.[1] In the reactions with the ferrocenylphosphines and o-(thiomethoxymethyl)phenyldiphenylphosphine, the colored aliquots were titrated by use of an Aminco-Cotlove Automatic Chloride Titrator.

Kinetics Procedure for the Reactions of Aryldiethylphosphines with Ethyl Iodide in Acetone. The procedure of Henderson and Buckler[3] was followed. The titrations were carried out by the Volhard method.

Preparation of Triarylarsines. Triphenylarsine, mp 59–60 °C (reported[42] mp 61 °C), tri-p-anisylarsine, mp 156–158 °C (reported[43] mp 158 °C), and tri-o-anisylarsine, mp 201.5–203.0 °C (reported[44] mp 200 °C), were prepared by the Wurtz-type reaction described in "Organic Syntheses".[42] Tri-p-tolylarsine, mp 148–150 °C (reported[45] mp 146 °C), tri-o-tolylarsine, mp 110–112 °C (reported[46] 108–109 °C), tri-p-chlorophenylarsine, mp 113–114 °C, and tri-p-bromophenylarsine, mp 140–141 °C, were prepared by the diazonium salt procedure of Hanby and Waters.[47]

Anal. Calcd for $C_{18}H_{12}AsCl_3$: C, 52.78; H, 3.95; As, 18.29. Found: C, 53.14; H, 3.30; As, 18.32.

Anal. Calcd for $C_{18}H_{12}AsBr_3$: C, 40.20; H, 2.23; As, 13.97; Br, 44.60. Found: C, 39.78; H, 2.32; As, 14.00; Br, 44.69.

Analysis of Triarylarsines. An accurately weighed sample of the arsine (ca. 0.4 mmol) was dissolved in 10.00 ml of chloroform and titrated with a standardized 0.050 M solution of bromine in glacial acetic acid. The end point was determined by use of a pH meter equipped with glass and platinum electrodes. It was necessary to

Table VI. Properties of Quaternary Phosphonium Halides

Phosphonium cation	Anion	Cryst solvent	Mp, °C	Reported mp, °C	Anal.[a]	NMR, δ ($CDCl_3$)[b] (J, Hz)
o-Tolyldiphenylbenzyl	Cl^-	EtOH–AcOEt	280–283 dec	280–283 dec[34]	C, H, P, Cl[34]	2.17 s, 5.32 d (J = 15)
p-Tolyldiphenylbenzyl	Cl^-	EtOH–AcOEt	246–248 dec	246–248 dec[34]	C, H, P, Cl[34]	2.52 s, 5.64 d (J = 15)
o-(Methoxymethyl)phenyldiphenylbenzyl	Cl^-	$CHCl_3$–ether	252–254		P	2.98 s, 4.40 s, 5.58 d (J = 15)
p-(Methoxymethyl)phenyldiphenylbenzyl	Cl^-	$CHCl_3$–ether	214–217		P	3.60 s, 4.79 s, 5.67 d (J = 14.5)
o-Thiomethoxyphenyldiphenylbenzyl	Cl^-	$CHCl_3$–ether	240–243		P	2.37 s, 5.68 d (J = 15)
p-Thiomethoxyphenyldiphenylbenzyl	Cl^-	EtOH–AcOEt	220–222		P	2.64 s, 5.51 d (J = 15)
o-(Thiomethoxymethyl)-phenyldiphenylbenzyl	Cl^-	$CHCl_3$–ether	234–236		P	1.80 s, 3.51 s, 5.76 d (J = 14.5)
Ferrocenyldiphenylbenzyl	Cl^-	EtOH–ether	178–179		C, H, Cl, P	5.02 d (J = 14)
Diferrocenylphenylbenzyl	Cl^-	EtOH–ether	205–206		C, H, Cl, Fe	
Phenyltriethyl	I^-	EtOH–AcOEt	141–142	140–141[3]		1.28 d of t (J_{PH} = 18, J_{HH} = 7.5), 2.93 d of q (J_{PH} = 13, J_{HH} = 7.5)
o-Anisyltriethyl	I^-	EtOH–AcOEt	193–194		C, H, I, P	4.1 s, 1.26 d of t (J_{PH} = 18, J_{HH} = 7.5), 2.82 d of q (J_{PH} = 13, J_{HH} = 7.5)
m-Anisyltriethyl	I^-	EtOH–AcOEt	154–155		C, H, I, P	4.0 s, 1.29 d of t (J_{PH} = 18, J_{HH} = 7.5), 2.95 d of q (J_{PH} = 13, J_{HH} = 7.5)
p-Anisyltriethyl	I^-	EtOH–AcOEt	140–141		C, H, I, P	3.92 s, 1.29 d of t (J_{PH} = 18, J_{HH} = 7.5), 2.87 d of q (J_{PH} = 13, J_{HH} = 7.5)

[a] Found values were within ±0.3% of calculated values. [b] δ (7.0–8.0, m) for aromatic protons not listed.

obtain a titration curve, millivolts being plotted against milliliters. This method was also used to check the purity of the arsines, the respective molecular weights being found to agree within ±2 units with the calculated values.

Kinetics Procedure for Reactions of Triarylarsines with Benzyl Bromide. Contained in an accurately tared 50-ml volumetric flask, an accurately weighed sample of benzyl bromide (approximately 0.09 mol) was diluted with spectral grade chloroform to within 1 cm of the mark. The flask was allowed to equilibrate in a constant-temperature bath for several hours and then filled to the mark with thermally equilibrated chloroform, mixed thoroughly, and replaced in the bath.

An accurately weighed sample of a triarylarsine (exactly one-tenth the mole quantity of the benzyl bromide) was weighed in a tared 50-ml Erlenmeyer flask. The arsine was dissolved in spectral grade chloroform, transferred to a 100-ml volumetric flask, diluted to a point 1 cm below the flask's neck, and allowed to equilibrate overnight in the constant-temperature bath.

A 5.00-ml sample of the benzyl bromide–chloroform solution was transferred to the flask containing the equilibrated arsine solution, diluted to the mark with thermally equilibrated chloroform, and mixed thoroughly. With the mark on the neck of the volumetric flask showing just above the water level, the volume within the flask was adjusted if necessary. Concentrations of both reactants were approximately 0.09 M.

A 5.00-ml pipet was used to transfer each 5.0-ml aliquot into a 50-ml beaker containing 5 ml of chloroform. The unreacted arsine was titrated with a standard solution of bromine (0.05 M) in glacial acetic acid as described previously.

All concentrations of tri-o-anisylarsine were approximately 0.045 M because of its low solubility.

The titer of the bromine–acetic acid solution changes slowly, necessitating daily standardizations against three samples of triphenylarsine.

Determination of Equilibrium Constants. A solution of 1.9287 g (1.1278 mmol) of benzyl bromide in chloroform was added to a 25-ml volumetric flask containing 1.13 mmol of the triarylphosphine (0.565 mmol in the case of tri-o-anisylarsine). After dilution to the mark with chloroform, the solution was allowed to stand at room temperature for 10 months. Then it was placed in a constant-temperature bath maintained at 29.63 °C for 2 weeks. Duplicate 5.00-ml aliquots of the solution were titrated for unreacted triarylarsine as described previously.

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Registry No.—Ethyl iodide, 75-03-6; benzyl chloride, 100-44-7; benzyl iodide, 100-39-0; o-bromobenzyl methyl ether, 52711-30-5; chlorodiphenylphosphine, 1079-66-9; m-anisyldichlorophosphine, 58325-48-7; m-bromoanisole, 2398-37-0; phosphorus trichloride, 7719-12-2; diethyl ether, 60-29-7; o-anisyldichlorophosphine, 58325-49-8; p-anisyldichlorophosphine, 19909-85-4; tri-p-chlorophenylarsine, 17314-57-7; tri-p-bromophenylarsine, 6306-93-0.

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Carbon-13 Nuclear Magnetic Resonance Spectroscopy in the Study of Conformational Effects among Cyclohexyl Phosphorus Compounds

Michael D. Gordon and Louis D. Quin*

Department of Chemistry, Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706

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^{13}C NMR spectra were obtained for the cis and trans isomers resulting from situating each of the following functions at the 4 position of *tert*-butylcyclohexane: PH_2, PMe_2, PCl_2, $P(OMe)_2$, $PSMe_2$, $^+PMe_3I^-$. For the trans isomers, the ^{13}C spectra were consistent with diequatorial substitution. In the cis isomers, the trivalent functions occupied the normal axial position but the larger $PSMe_2$ and $^+PMe_3$ groups, as seen from chemical shift effects, caused considerable distortion of the ring, either through flattening about the 1,4-ring carbons or by adoption of a twist conformation. C–P coupling constants favor the former explanation. When $PSMe_2$ and $^+PMe_3$ are placed in the cis 4 position of methylcyclohexane, the ^{13}C NMR evidence suggests that they adopt the equatorial position and force methyl into the axial position. A minimum *A* value for these phosphorus functions derived from this information is 3.0 kcal/mol. The PMe_2 group has an *A* value similar to that for methyl, and the ^{13}C NMR spectrum for the 1,4 cis isomer is consistent with an approximately 1:1 mixture of equilibrating conformers. Among the trivalent functions, the three-bond ^{13}C–^{31}P coupling constant was found to be under strong steric control for the primary phosphines alone; the other functions showed only a small difference in $^3J_{PC}$ between the cis and trans isomers. The spectra of 24 cyclohexane derivatives were recorded during this study and interpreted by existing generalities.

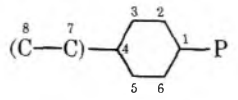
^{13}C NMR spectroscopy is firmly established as a technique providing valuable information about conformational aspects of six-membered rings.[2,3a] We have now applied it in a systematic way to cyclohexanes containing various phosphorus functions and report our results in this paper.[4] We have done this first to test the validity of our *A* values for some trivalent functions, which we have recently determined by ^{31}P NMR spectroscopy,[5] and then to obtain qualitative information on some tetravalent phosphorus functions, which could not be determined by the ^{31}P approach used. Since the trivalent groups studied [PH_2, PCl_2, PMe_2, and $P(OMe)_2$] all had sizable *A* values (±0.2 kcal/mol of that for methyl,[7] 1.7), it might be expected that tetravalent functions would show even larger values, indeed possibly approaching that of *tert*-butyl. A precise value for this group is still lacking but the range 4–5 kcal/mol has been proposed.[7,8]

^{13}C Spectral Data and Assignments. All data for the 24 compounds studied are recorded in Table I. For measurements on cis, trans isomers (whose structures have been determined in previous work[5]), data were obtained on samples enriched in the pertinent form, in some cases as high as 95%. Assignments are easily made on the following lines: (1) C-1 and C-4 are of half the intensity of C-2,6 and C-3,5. C-1 is always a doublet through coupling to ^{31}P; C-4 shows no coupling. (2) Methyls on phosphorus are always the most upfield doublets. (3) Methyls on C-4 are the most shielded of the uncoupled carbons, and are of unit intensity. (4) *tert*-Butyl carbons are recognized from their intensities (weak quaternary signal, strong methyl signal) and near identity of position in both cis and trans forms. (5) Differentiation between C-2,6 and C-3,5 was based on a combination of shift and P–C coupling effects. For PH_2, the differentiation is easy; C-2,6 are well downfield (δ 36.0) of C-3,5 (27.4) since the former carbons feel a strong β effect due to phosphorus, while the latter carbons are not greatly shifted from the cyclohexane value (27.7). The same effect is seen for NH_2[9] (δ $C_{2,6}$ 37.7; δ $C_{3,5}$ 25.8). For all other phosphorus functions, the atoms replacing hydrogen can be expected to exert an additional upfield γ effect at C-2,6, compensating in part for the β effect acting in the opposite direction. As a result signals for C-2,6 move closer to those for C-3,5, as is true in many cyclohexyl derivatives.[9] We have reported on the same effect in noncyclic phosphorus derivatives.[10] To distinguish between these carbons, P–C coupling constants were used. Among the noncyclic trivalent derivatives, ^2J is larger than ^3J, and the values found for the cyclohexyl derivatives were very similar to those seen for *n*-butyl derivatives.[10] For the tetravalent functions, ^3J is considerably larger than ^2J in the *n*-butyl series,[10] and comparable values were obtained for the cyclohexyl derivatives.

For derivatives bearing trans 4-alkyl substituents, assignments were straightforward; shift effects occurred that resembled closely those seen on placing the same alkyl group on cyclohexane. For the cis derivatives, additional effects are present owing to the placement of one group in the axial position; these effects are more appropriately discussed in later sections of this paper.

Effects of Phosphorus Functions on the Carbon Signals of Cyclohexane. It is known from our previous studies based on ^{31}P NMR spectroscopy[5] that the six phosphorus functions are of considerable size ($A > 1.5$ kcal/mol) and will occupy the equatorial position on cyclohexane to a very large extent. Therefore, spectra for monosubstituted cyclohexanes can be taken as arising from the equatorial conformers. The shifts caused by these equatorial phosphorus substituents on the cyclohexane carbons are summarized in Table II in terms of α, β, γ, and δ effects at C-1, C-2,6, C-3,5, and C-4, respectively.

Table I.[a] ^{13}C NMR Spectral Data



Compd	Identity of 4 substituent	C-1	C-2,6	C-3,5	C-4	P–CH_3	C-7	C-8
			A. Primary Phosphines (P = PH_2)[b]					
1	H	27.2 (6)	36.0 (7)	27.4 (8)	25.9			
2	*trans*-*t*-Bu	27.2 (7)	36.6 (7)	28.5 (9)	47.3		32.2	27.6
3	*cis*-*t*-Bu	23.5 (9)	32.7 (8)	21.8 (2)	48.5		32.4	27.5
			B. Tertiary Phosphines (P = PMe_2)[c]					
4	H	39.3 (8)	28.9 (14)	27.0 (10)	26.0	11.3 (15)		
5	*trans*-Me	39.2 (7)	29.1 (14)	36.1 (11)	32.2	11.6 (17)	23.1	
6	*trans*-*t*-Bu	39.3 (9)	29.4 (14)	28.0 (11)	48.0	11.5 (15)	32.5	27.6
7	*cis*-Me	40.0 (9)	25.6 (12)	32.0 (8)	30.4	12.4 (15)	20.3	
8	*cis*-*t*-Bu	40.0 (10)	28.9 (11)	23.5 (8)	49.0	13.1 (15)	32.8	27.7
			C. Phosphonous Dichlorides (P = PCl_2)[b]					
9	H	48.5 (45)	25.6 (16)	26.0 (11)	25.8			
10	*trans*-*t*-Bu	48.4 (45)	26.0 (16)	27.1 (11)	47.4		32.2	27.4
11	*cis*-*t*-Bu	49.3 (44)	27.3 (15)	23.8 (9)	48.4		32.6	27.6
			D. Dimethyl Phosphonites (P = $P(OMe)_2$)[b]					
12	H	41.3 (15)	25.6 (17)	26.7 (11)	26.9	[54.0 (14)][d]		
13	*trans*-*t*-Bu	41.0 (14)	25.9 (17)	27.4 (9)	48.1	[53.9 (13)][d]	32.6	27.7
14	*cis*-*t*-Bu	38.2 (18)	26.7 (14)	24.5 (7)	48.8	[53.8 (13)][d]	32.7	27.7
			E. Phosphine Sulfides (P = $PSMe_2$)[c]					
15	H	41.1 (54)	25.6 (3)	26.2 (14)	25.7	18.5 (52)		
16	*trans*-Me	40.7 (54)	25.7 (~2)	34.8 (15)	32.1	18.6 (55)	22.6	
17	*trans*-*t*-Bu	41.2 (53)	26.4 (3)	27.3 (13)	47.5	18.6 (52)	32.6	27.6
18	*cis*-Me	41.0 (54)	19.8 (~2)	31.5 (14)	26.6	18.6 (55)	17.4	
19	*cis*-*t*-Bu	36.7 (51)	24.9 (2)	23.2 (4)	46.0	21.0 (53)	32.7	27.5
			F. Phosphonium Iodides (P = $^+PMe_3I^-$)[c]					
20	H	32.0 (52)	25.1[e]	25.5 (15)[e]	25.1[e]	7.5 (52)		
21	*trans*-Me	31.7 (51)	25.2 (~2)	34.0 (14)	31.6	7.6 (53)	22.5	
22	*trans*-*t*-Bu	32.1 (51)	25.8 (3)	26.5 (15)	47.2	7.8 (55)	32.6	27.6
23	*cis*-Me	32.0 (52)	19.7 (~2)	30.9 (13)	26.2	7.6 (53)	17.5	
24	*cis*-*t*-Bu	29.2 (48)	24.2 (2)	23.8 (4)	45.6	10.0 (52)	32.7	27.4

[a] Chemical shifts in parts per million downfield from internal Me_4Si. Values in parentheses are P–C coupling constants (Hz), where observed. [b] Neat samples. [c] $CDCl_3$ solutions. [d] Values for CH_3–O. [e] Severe peak overlap did not allow accurate determination of coupling constants.

Table II. Chemical Shift Effects on the Cyclohexane Ring by Equatorial P Substituents[a]

	α	β	γ	δ
PH_2	−0.5	+8.3	−0.3	−1.8
PMe_2	+11.6	+1.2	−0.7	−1.7
PCl_2	+20.8	−2.1	−1.7	−1.9
$P(OMe)_2$	+13.6	−2.1	−1.0	−0.8
$PSMe_2$	+13.4	−2.1	−1.5	−2.0
$^+PMe_3$	+4.3	−2.6	−2.2	−2.6

[a] Negative signs refer to shielding, positive to deshielding, of the carbons of cyclohexane (δ 27.7) on replacement of H by the P function.

Of the various substituents, all but PH_2 and $^+PMe_3$ have been studied previously with regard to their effects on the carbons of *n*-butane.[10] In general, effects on cyclohexane are similar in kind.

In our previous work on noncyclic compounds,[10] it was found that PMe_2, PCl_2, $P(OMe)_2$, and $PSMe_2$ groups exert large, quite different deshielding effects on α carbons, but have negligible effects on β carbons owing to the compensating shielding γ effect by the atoms attached directly to the phosphorus. On examining data for the cyclohexyl compounds, the same effects are apparent at the α and β positions. The $^+PMe_3$ group falls in the same category, although it has, as expected,[11] a significantly smaller α effect than do the other groups. The PH_2 group causes shielding of the carbon of methylphosphine by 2.3 ppm relative to methane, presumably through its electron-releasing inductive effect relative to carbon.[3b] In the cyclohexyl derivative, its α effect is negligible. The deshielding β effect is substantial; indeed it is the largest β effect (8.3 ppm) of any phosphorus group so far examined, with a magnitude comparable to that[2] for $-CH_3$ (8.4), NH_2 (10.1), and OH (8.4). The small α value for PH_2 relative to PMe_2 is easily explained by the presence in the latter of deshielding β effects by the methyl groups.

γ effects (shielding) felt at C-3,5 of the cyclohexane ring are quite small, but detectable, and indeed are of very similar magnitude to γ effects seen on C-3 of *n*-butyl chains.[10] (As will be noted later, larger γ effects are found in derivatives where the phosphorus group is in the axial position, where steric involvement with C-3,5 is pronounced.)

At C-4 of the cyclohexane ring, all six phosphorus functions cause a small (1–3 ppm) upfield shift. This δ effect is quite characteristic of a number of common substituents.[9] The opposite effect occurs in noncyclic compounds where the δ effect is weakly deshielding.[2,12] As observed by others,[13] the δ effect in the cyclohexanes does not correlate well with substituent polarity or size; the δ effect for PH_2 (1.8 ppm) is as large as that for PMe_2 (1.7) and larger than that (0.8) for the

more polar $P(OMe)_2$ group. However, the tetravalent functions have relatively large δ effects ($PSMe_2$, 2.0; $^+PMe_3$, 2.6).

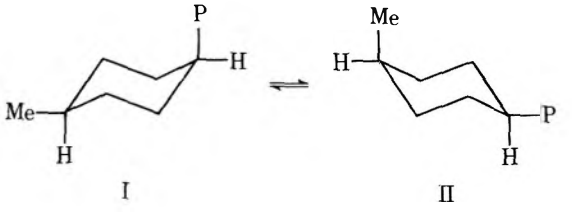
^{13}C Spectra of *trans*-4-Alkylcyclohexyl Phosphorus Compounds. When methyl or *tert*-butyl are substituted for hydrogen at the 4 position of the cyclohexyl phosphorus compounds, no significant changes in ^{13}C shifts for C-1 occur. To illustrate, in the PMe_2 series values for C-1 are 39.3 (**4**, 4-H), 39.2 (**5**, 4-Me), and 39.3 (**6**, 4-*t*-Bu); similar data are found in Table II for the other functions. It is also noticed that methyls on phosphorus, where present, have chemical shifts independent of 4 substituents (e.g., for **4**, 11.3; **5**, 11.6; **6**, 11.5). These observations are consistent with a conformation for all compounds where the P substituent is predominantly in the equatorial position, for any significant amount of axial conformer would have led to noticeable ^{13}C changes. These changes are seen on comparison of the trans isomers with the cis isomers, discussed in the next section.

Eliel et al.[13] have recently pointed out the operation of a shielding effect at γ carbons by substituents held rigidly in the anti-periplanar relation. In cyclohexanes, the effect is felt at C-3,5 by substituents in the equatorial position. Our series of 4-*tert*-butyl compounds allows an extension of Eliel's considerations to anti-periplanar phosphorus substituents. We would expect from Eliel's generalizations that the effect will be quite small, for data so far available suggest the effect to be stronger for substituents based on second-row than for third-row elements. This is indeed what we observe. The $\gamma_{anti\text{-}periplanar}$ shielding constants for the phosphorus functions, derived from the data of Table II by comparing shifts for C-3,5 to that for the same carbons in *tert*-butylcyclohexane (δ 28.0), are as follows (where − is shielding, + is deshielding): PH_2, +0.5; PMe_2, 0.0; PCl_2, −0.9; $P(OMe)_2$, −0.6; $PSMe_2$, −0.7; $^+PMe_3$, −1.5. Only the last value approaches the size normally seen for second-row substituents[13] (NH_2, −1.6; others are in the range −1.6 to −2.7); the others are significantly smaller, and the PH_2 group even appears to exert a small $\gamma_{anti\text{-}periplanar}$ *deshielding* effect.

^{13}C Spectra of *cis*-4-Alkylcyclohexyl Derivatives. With Trivalent Phosphorus Functions. The *A* values for the trivalent phosphorus functions as determined by ^{31}P NMR spectroscopy[5] are considerably smaller than that for *tert*-butyl (4–5 kcal/mol), and consequently these functions are forced into the axial position by a cis 4-*tert*-butyl group. The ^{13}C spectra are convincing as proof of this statement, especially through the pronounced upfield shift at C-3,5 seen on comparing cis to trans. These gauche γ shifts vary with the function, but are in the range (3–7 ppm) in which are found most common organic groups.[2,14] The magnitude of this type of γ shift does not correlate well with group size or *A* value,[14] and it is not surprising to find PH_2 with the greatest gauche γ effect (6.7). The steric differences in axial vs. equatorial conformers are also known to have influence on C-1 chemical shifts, but not always in predictable ways.[14] The phosphorus functions show this uncertainty; no correlation with either size or direction of the shifts seems to exist. This is seen to be true also for C-2,6. At C-4, however, the axial groups are consistently associated with downfield shifts (0.7–1.2 ppm) relative to the equatorial groups. Finally, it is noted that the methyls of PMe_2 are more deshielded (1.6 ppm) when in the axial conformation. Crowding of axial PMe_2 with C-3,5 therefore can be said to produce a downfield effect at methyl; this constitutes another[15] exception to the generality that crowding causes upfield shifts.

The availability of derivatives of trivalent phosphorus functions with fixed geometry provides an opportunity for the first consideration in this oxidation state of the dependence on dihedral angles of ^{13}C–^{31}P coupling constants ($^3J_{PC}$) in the fragment PCCC.[16] For tetravalent functions, the steric influence on $^3J_{PC}$ is quite pronounced and appears to follow a Karplus-type relation.[17] In the cyclohexane system, larger coupling would be expected for trans isomers (dihedral angle about 180°) than for cis isomers (dihedral angle about 60°), and, as will be discussed in a later section, this is exactly what we have observed for the tetravalent functions $PSMe_2$ and $^+PMe_3$. However, only one of the four trivalent functions displayed this property; for PH_2, $^3J_{PC}$ of the trans isomer was 9 Hz, but only 2 Hz for the cis isomer. For the other functions, the values were quite similar, although for each the trans value was slightly the larger (PMe_2 trans 11, cis 8 Hz; PCl_2 trans 11, cis 9 Hz; $P(OMe)_2$ trans 9, cis 7 Hz). This result is quite surprising, pointing as it does to a role for the structure about the phosphorus atom in determining the magnitude of the steric control on $^3J_{PC}$. However, another case can be cited where a role for the oxidation state of phosphorus is seen. In a noncyclic system an increase in the number of carbons that can occupy gauche positions relative to phosphorus as bond rotation occurs necessarily decreases the averaged value for the dihedral angle derivable from the various conformations. If a Karplus-like relation prevails, then $^3J_{PC}$ should be smaller for the branched-chain compound. This is indeed observed[10] on comparing tri-*n*-butylphosphine sulfide ($^3J_{PC}$ = 16 Hz) to triisobutylphosphine sulfide ($^3J_{PC}$ = 9 Hz). It is *not* observed[10] on comparing tri-*n*-butylphosphine ($^3J_{PC}$ = 10 Hz) to triisobutylphosphine ($^3J_{PC}$ = 10 Hz). On the other hand, $^3J_{PC}$ in tertiary phosphines where phosphorus is conformationally constrained in a six-membered ring[18] (hence with dihedral angle about 60°) is quite small (2–3 Hz), and not at all consistent with the value observed here (8 Hz) for the freely rotating PMe_2 group with a similar dihedral angle (8). Further experimental exploration of this structure-dependent three-bond coupling phenomenon is called for.

When methyl is present as the 4 substituent on the cyclohexane ring, it would be expected that the conformational equilibria would have nearly equal amounts of conformers I and II, since methyl and the trivalent phosphorus functions have rather similar *A* values. The ^{13}C shifts should therefore

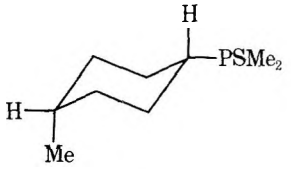


I II

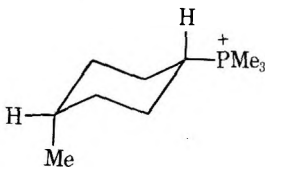
be averaged for the values of each conformation, as was found to be true for ^{31}P shifts.[5] To test for this effect, the spectrum of the cis PMe_2 derivative (**7**) was compared with that of the trans (**5**) where both substituents are equatorially disposed. The 4-methyl signal provides the clearest indication of the existence of the equilibrium in the cis isomer, for methyl is known to have a chemical shift when equatorial on the cyclohexane ring (23.5 ppm) that is quite different from that when axial (17.6 ppm).[19] These values are not influenced significantly by the presence of a 4 substituent.[19b,20] The value for trans isomer (**5**) is of the expected magnitude (δ 23.1) for equatorial disposition, but that for the cis isomer (**7**) (δ 20.3) is between the extremes, as would be expected for the proposed[5] equilibrium with $K \sim 1$. A similar effect is present for methyls of Me_2P; the deshielding (0.8 ppm) of these carbons in the cis isomer (**7**) relative to the trans (**5**) is half of that when this group is purely axial as in the cis 4-*tert*-butyl compound **8** (1.6 ppm downfield of trans **6**). Effects are also noticed at C-2,6 as well as C-3,5; substantial upfield shifts occur in the cis isomer since both types of carbons feel increased crowding with axial 4-CH_3 and PMe_2, respectively.

Tetravalent Phosphorus Functions. The presence of the larger tetravalent phosphorus functions ($^+PMe_3$ and $PSMe_2$)

makes a profound difference on the ^{13}C spectra of 4-methylcyclohexyl derivatives. As had been earlier indicated by our ^{31}P NMR spectra,[5] these groups must have *A* values well in excess of that for CH_3 (1.7 kcal/mol) for the spectra give the expected indications of 4-CH_3 being forced into the axial position. Thus, the 4-CH_3 in the cis isomer of the sulfide (**18**) is 5.2 ppm upfield of that in the trans (**16**); for the phosphonium salt, the difference is 5.0 ppm (**23** vs. **21**). These values leave no doubt that the methyl is very largely in the axial position (cf. 5.9-ppm difference for axial and equatorial methyl in *cis*-1,4-dimethylcyclohexane at 180 K).[19b] Changes of similar magnitude are expected also at C-4, and are observed (sulfide 5.5, salt 5.4 ppm). Other spectral changes [upfield shifts at C-2,6 and C-3,5 and similarity of the sterically dependent (vide infra) values for $^3J_{PC}$] are also entirely consistent with the assignment of structures **25** and **26** as best representing



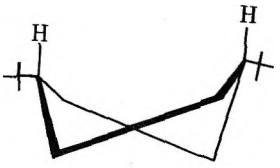
25



26

the conformation of these phosphorus compounds. Although spectral evidence does not define the contribution of the minor conformer with equatorial methyl–axial P function, an estimate that 10% is present seems reasonable and leads to an equilibrium constant ($ax_P \rightleftharpoons eq_P$) of 9, and a free energy difference of −1.3 kcal/mol. By the principle of additivity,[21] extracting the $\Delta G°$ value for CH_3 of −1.7 kcal/mol leads to an *A* value ($-\Delta G°$) of 3.0 kcal/mol for the two phosphorus functions. We therefore propose this as a minimum *A* value which is consistent with the data so far available; the value could, of course, be significantly larger.

The *A* values for the tetravalent phosphorus functions therefore stand among the largest yet reported for a nonalkyl or nonaryl substituent.[7,8] Accordingly, they should compete with the *tert*-butyl group for the equatorial position when placed in the cis 4 orientation. To look for this effect in the ^{13}C spectra, attention should first be given to the case of the *cis*-1,4-di-*tert*-butylcyclohexane system. In a chair conformation axial character for one of the *tert*-butyls is a requirement; alternatively, ring distortion may be so great as to induce adoption of the twist conformation[22,23] as in **27**. The ^{13}C data



27

for this compound[24] show no significant change for the quaternary or methyl carbons of the butyl group relative to the trans isomer, but do show upfield shifts at *C*-butyl (5.6 ppm) and the methylene carbons (4.3 ppm) in the cis isomer. These shifts clearly reveal the increased steric crowding in the cis isomer but do not necessarily imply that a change from the general chair shape to a twist shape has occurred, although ^1H NMR data are interpreted to be more indicative of such a change.[22] As an alternative to a twist conformation, a chair flattened at both ends needs also to be considered; such a structure has indeed been determined by x-ray analysis for *cis*-1-*p*-bromophenyl-4-*tert*-butylcyclohexane.[25] On comparing the cis phosphorus compounds **19** and **24** to the trans isomers (**17** and **22**), it is found that pronounced upfield shifts have occurred at all ring positions in the cis isomers, but seem to be the largest at atoms more controlled by the P function than by butyl. To illustrate, in the cis sulfide (**19**) C-1 is shifted 4.5 ppm upfield of the trans, and C-3,5 which would experience γ-gauche shielding by an axial P substituent are shifted 4.1 ppm upfield. At C-2,6, which are γ to butyl, an upfield shift occurs, but it is small (1.5 ppm). C-4 requires special consideration. In all of the cis isomers of the trivalent P functions, C-4 experiences a deshielding of 0.7–1.2 ppm. Since the δ effect of the tetravalent functions in the monosubstituted compounds (Table II) is in the same direction as for the trivalents, it might be expected that C-4 in the cis *tert*-butyl compounds with tetravalent phosphorus should also go downfield. In fact, the opposite is seen; C-4 is shifted *upfield* by 1.5–1.6 ppm. We attribute this to marked displacement of *tert*-butyl from the usual equatorial position, since it is just this sort of chemical shift change that is seen for *cis*-1,4-di-*tert*-butylcyclohexane. The net effect at C-4 is therefore larger than 1.5–1.6 ppm, and probably is as large as 2–3 ppm. Since this is, very roughly, about half of the shift seen at the comparable carbon in the di-*tert*-butyl compound, it is implied that the P functions have somewhat smaller *A* values than the *tert*-butyl group, consistent with our proposal of a minimum *A* value of 3.0 for the former. Crowding in the cis isomers of the sulfide and salt also produces a pronounced downfield shift in the *P*-methyl signals (2.4 and 2.2 ppm, respectively). The same effect was pointed out for the $-PMe_2$ group, although the magnitude is smaller (1.6 ppm).

The coupling of C-3,5 with ^{31}P sheds additional light on the conformational differences between the cis and trans forms of these compounds. This coupling is large in the trans forms **17** and **22** (13–15 Hz) and small (4 Hz) in the cis forms **19** and **24**. This clearly indicates that a considerable difference in the dihedral angle relating P to C-3,5 must be present.[17] This angle is 180° in the trans isomer in an ideal chair with ring dihedral angles of 60°. For the cis isomer, a regular chair conformation with axial P substituent results in a dihedral angle of 60°. If the cis isomer adopted a twist conformation, that with minimal nonbonded interaction would be represented by the counterpart of **27**. In this twist conformation, the dihedral angle relating P to C-3 is not the same as that relating P to C-5; in an ideal structure, one angle is 153° while the other is 169°.[26] Only the adoption of another, more crowded twist conformation than **27** would produce significantly smaller dihedral angles. At this time, the coupling evidence seems to point away from a twist conformation for the cis isomers and toward a chair conformation with axial P substituent, probably with alleviation of crowding by flattening of the ring at both ends as was found for 1-*p*-bromo-4-*tert*-butylcyclohexane.[25] With further general development of the knowledge of $^3J_{PC}$ dependence on angle relations among phosphine sulfides and phosphonium salts, it should, in principle, be possible to be more precise in the definition of the molecular geometry of these cis forms.

Experimental Section

General. Proton decoupled ^{13}C spectra were obtained at 22.62 MHz on a Bruker HFX-10 system using the Fourier transform technique. Hexafluorobenzene in a 3-mm coaxial capillary insert served as a heteronuclear lock. Chemical shifts were determined from internal tetramethylsilane to ±0.1 ppm, while ^{13}C–^{31}P coupling constants are reported to ±1 Hz. Trivalent phosphorus compounds, except for the tertiary phosphines, were run as neat liquids. All other compounds were examined in $CDCl_3$ solution.

Compounds. The synthesis, properties, and ^{31}P chemical shifts of all compounds of this study have been reported elsewhere.[5] The ^{13}C NMR spectra for the series of *trans*-4-*tert*-butyl derivatives were obtained on isomer mixtures enriched to about 80–95% in this form. For phosphonous dichlorides **10** and **11**, this was accomplished by fractional distillation to give 80% trans (**10**) form. This mixture then gave similarly trans-enriched phosphines (**2** and **3**) on reduction and phosphonites (**13** and **14**) on methanolysis. Tertiary phosphines **6** and **8** were formed on reaction of the 4-*tert*-butylcyclohexyl Grignard

reagent with Me_2PCl, with **6** constituting about 85–90% of the mixture. This ratio was maintained on sulfurization to form **17** and **19**, and methylation to **22** and **24**. Fractional distillation of the phosphonous dichlorides also provided a sample enriched to about 80% in the *cis* isomer (**11**) and this was used to form the entire series of *cis* compounds by conventional reactions.[5] For the 4-methylcyclohexyl series, a trans-rich (80–90%) tertiary phosphine mixture (**5** and **7**) resulted from the Grignard reaction, and this led to sulfide (**16** and **18**) and salt (**21** and **23**) mixtures similarly enriched. Data for the *cis*-4-methylcyclohexyl series were obtained on mixtures of nearly 1:1 *cis*–*trans* composition.

Registry No.—**1**, 822-68-4; **2**, 58359-91-4; **3**, 58359-90-3; **4**, 58359-87-8; **5**, 58403-25-1; **6**, 58359-93-6; **7**, 55615-34-4; **8**, 58359-92-5; **9**, 2844-89-5; **10**, 58359-95-8; **11**, 58359-94-7; **12**, 16195-98-5; **13**, 58359-97-0; **14**, 58359-96-9; **15**, 58359-88-9; **16**, 58360-05-7; **17**, 58359-99-2; **18**, 58360-04-6; **19**, 58359-98-1; **20**, 58359-89-0; **21**, 58360-07-9; **22**, 58448-99-0; **23**, 58360-06-8; **24**, 58449-00-6.

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Organometallic Chemistry. 9.[1] Carbon-13 Nuclear Magnetic Resonance Study of the Cumylchromium Tricarbonyl and of Cycloheptatrienylmolybdenum (-chromium, and -tungsten) Tricarbonyl Cations

George A. Olah* and Simon H. Yu[2]

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106

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The cumylchromium tricarbonyl cation was prepared under long-lived ion conditions, and studied by NMR (^1H and ^{13}C) spectroscopy. For comparison, the carbon-13 NMR parameters of three cycloheptatrienyl–$M(CO)_3$ cations (M = Mo, Cr, and W) were also determined and are reported. Based on the ^{13}C NMR studies the origin of the unusual stabilization of the cumylchromium tricarbonyl ion is discussed. The σ^+ substituent constant for the $Cr(CO)_3$ group and the fraction of the unit positive charge transmitted into the $M(CO)_3$ groups were qualitatively estimated.

The substituent effect of the metal tricarbonyl moiety in metal–arene complexes is of substantial interest. There is considerable evidence to show that π-complexed $Cr(CO)_3$ group exerts a net electron-withdrawing effect from the aromatic ring.[3] The deprivation of π-electron density on the aromatic ligand upon complexation with the $Cr(CO)_3$ group also appears to attenuate the substituent effect of other aryl substituents. On the other hand, the electron-releasing effect of the $Cr(CO)_3$ group has been demonstrated by the rate enhancement of solvolysis of tricarbonylchromium complexes of benzyl,[4,5] cumyl,[5] and 2-benzonorbornenyl[6] derivatives, and the increase of the pK_R^+ value for the benzylchromium tricarbonyl cation.[7] They were explained by the increase of stability of the intermediate cation with the attachment of the $Cr(CO)_3$ moiety. Previous attempts at the isolation of benzyl-, diphenylmethyl-, and triphenylmethylchromium tricarbonyl cations from the corresponding alcohols failed.[4] Upon treatment with $HClO_4$ or HBF_4 in Ac_2O, the alcohols gave only rapid decomposition. We would like to report now the preparation of the cumylchromium tricarbonyl cation **1**, the first chromium tricarbonyl complexed arylalkyl cation observed under long-lived conditions, and its ^1H and ^{13}C NMR spectroscopic study. The results provide evidence for the unusual stabilization of **1** through charge delocalization into the $Cr(CO)_3$ group. For comparison, we also determined the ^{13}C NMR spectroscopic parameters of three known cycloheptatrienylium–$M(CO)_3$ cations **2** (M = Mo, Cr, and W). Cations **2** represent a cyclic six π electron aromatic system attached to a metal tricarbonyl group, whereas **1** represents a similar six π electron system substituted by an electron-deficient exocyclic carbenium ion grouping.

Results and Discussion

A dark-green solution of the cumylchromium tricarbonyl cation **1** was obtained upon treatment of a solution of the chromium tricarbonyl complex of cumyl alcohol with fluorosulfuric acid in SO_2 at −80 °C under dry nitrogen. The carbon-13 spectrum of **1** is shown in Figure 1 and the ^1H and ^{13}C NMR parameters are summarized in Tables I and II, respectively, together with the data of the corresponding ions

Table I. ^{1}H NMR Parameters of the Cumylchromium Tricarbonyl Cation and Related Cumyl Cations

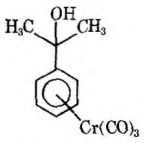
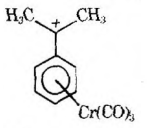
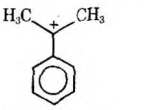
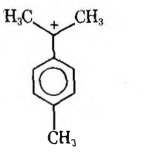
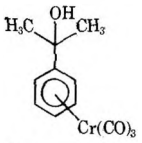
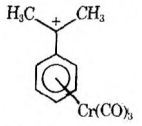
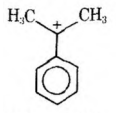
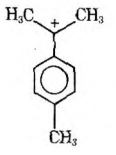
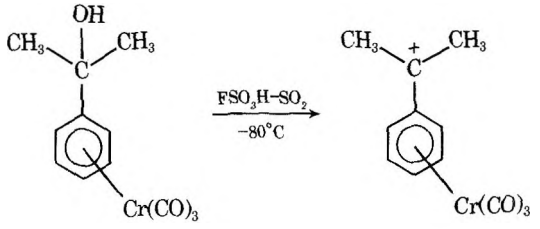
Registry no.	Compd	Ring protons	CH_3	OH
52409-32-2		5.37 (3 H), m 5.67 (2 H), m	1.58 (6 H), s	2.00 (1 H), s
58464-00-9		5.97 (3 H), m 5.32 (2 H), m	1.73 (6 H), s	
16804-70-9		8.73 (2 H) 7.82 (2 H) 8.42 (1 H)	3.48 (6 H)	
20605-66-7		8.72 (2 H) 7.40 (2 H)	3.12 (6 H)	

Table II. ^{13}C NMR Parameters of Cumylchromium Tricarbonyl Cation and Related Cumyl Cations

Compd	C_α	C_{ipso}	C_{ortho}	C_{meta}	C_{para}	CH_3	CO
	71.42	121.92	92.32	94.57	92.32	31.72	234.19
	170.92	101.66	99.49	120.67	96.72	24.74	228.39
	254.3	140.0	142.4	133.3	155.9	34.90	
	242.79	137.69	141.52	133.51	174.43	30.90	

and precursors. Noteworthy is that the benzylic carbon becomes deshielded upon ionization of the alcohol to **1**, but the shift is smaller compared to that observed in the corresponding parent, uncomplexed system. The significant shielding of the electron-deficient benzylic carbon in **1**, compared to that of the uncomplexed cumyl cation, indicates the unusual stabilization of the cumyl cation upon complexation and the extensive delocalization of charge through the whole complexed ion. However, the electron-deficient exocyclic carbon in **1** is more deshielded compared to that observed in the α-ferrocenylcarbinyl cation.[8] The carbon chemical shifts of **1** are overall shielded by 312.3 ppm compared to the uncomplexed cumyl cation. From this shielding about 200 ppm



1

is attributed to the change of the bonding nature upon complexation,[3] and the remaining 100 ppm corresponds to the transmission of ⅓ of the unit positive charge into the $Cr(CO)_3$ group, if the effects other than the development of charge are small. Recent carbon-13 spectroscopic study of benzylic carbocations showed that the carbon shifts reflected the trend of positive charge density distribution, correlating with the ability of substituents to delocalize positive charge and indicating the stability of ions.[9] Utilizing the observed Hammett type relationship between carbenium carbon shifts of substituted cumyl cations and Brown's σ^+ substituent constants,[10] a σ^+ value of -1.8 is estimated for the $Cr(CO)_3$ group (Figure 2).[9] Unlike the complexed benzyl and benzhydryl chlorides,[4] recent kinetic study on the rate of solvolysis of cumyl chloride–chromium tricarbonyl[5] indicated that the $Cr(CO)_3$ group is capable of enhancing the rate only by a factor of 28 and that it is comparative to a *p*-methyl group.[10] Since observed ΔH and ΔS values are much different from those of the uncomplexed system, it is proposed that a different mechanism is involved in the solvolysis of the chromium tricarbonyl complexed cumyl chloride.

Ions **2** were conveniently prepared by hydride abstraction from the corresponding cycloheptatriene–$M(CO)_3$ complexes

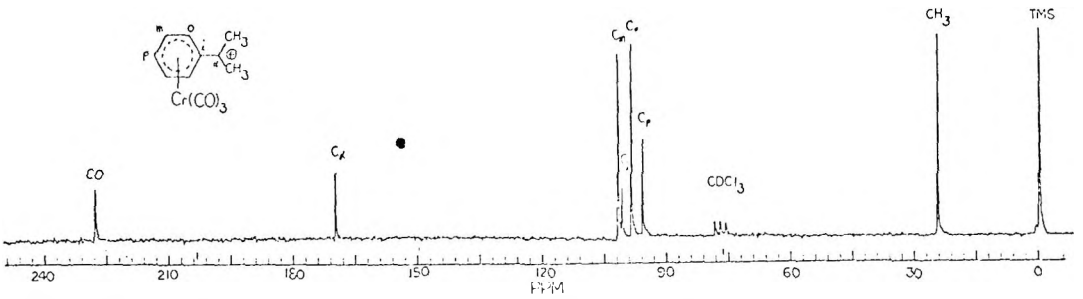


Figure 1. Carbon-13 spectrum of cumylchromium tricarbonyl cation in SO_2 at −70 °C.

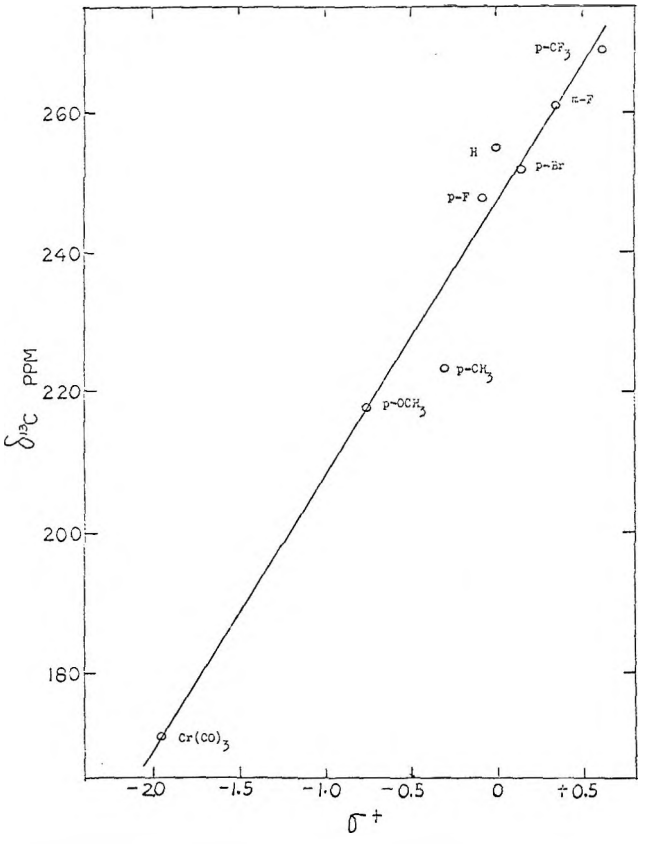
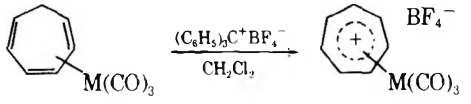


Figure 2. Correlation of carbenium carbon ^{13}C NMR chemical shifts to Brown's σ^+ substituent constants for substituted cumyl cations.



3a, M = Mo
b, M = Cr
c, M = W

2a, M = Mo
b, M = Cr
c, M = W

3 with triphenylcarbenium fluoroborate.[11] The ^{13}C NMR parameters of ions 2 and compounds 3 are summarized in Table III. Upon hydride abstraction, all ring carbons become equivalent as a single resonance and is deshielded. However, the deshielding effect is smaller compared to that observed for the corresponding uncomplexed tropylium ion indicating that the $M(CO)_3$ group also stabilizes the ions 2 by delocalizing charge. The almost identical deshieldings observed when compounds 3 are converted into 2 suggest that the molybdenum, chromium, and tungsten tricarbonyl groups have nearly equivalent stabilizing effects. The present data are also consistent with the previously determined pK_R^+ values of ions 2, which are almost identical, and are larger than that for the tropylium ion.[12] The chemical shifts of uncomplexed cycloheptatriene are overall deshielded by 284 ppm upon hydride abstraction, corresponding to development of unit positive charge. The difference of overall chemical shifts between **2b** and **3b** is 188 ppm. The deshielding is 96 ppm less than that of the uncomplexed, parent system and corresponds to ⅓ of the unit positive charge being transmitted into the $Cr(CO)_3$ group. It is interesting to compare this observation with cation **1**, where it is also estimated that ⅓ of the unit positive charge is transmitted. In the same manner, it is estimated that approximately ½ of the unit positive charge is transmitted into the $M(CO)_3$ groups in **2c** and **2a**.

The increase in shielding of the carbonyl resonance in **1** with respect to that of the corresponding alcohol and arenechromium tricarbonyls,[3] and **2a** with respect to that of **3a**, is consistent with the decrease of the electron density on the metal owing to transmission of charge to stabilize the cationic ligand.[13] It is also consistent with the decrease in the metal–carbonyl π back-donation with increasing carbonyl stretching frequencies.[11,12] Furthermore, the observation of a single resonance for the carbonyl carbons in **1** and **2a** points out the low rotational barrier of the $M(CO)_3$ group relative to the cationic ligand.

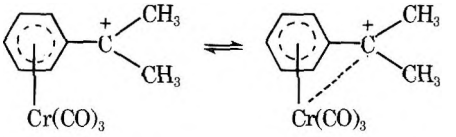
The bonding of the transition metal π complexes with olefinic ligands has generally been considered to be composed of a σ forward donation arising from an overlap of the filled bonding π orbital of the ligand with vacant orbitals of the metal and a π back-donation from an overlap of a filled d orbital of the metal with the antibonding π orbital of the ligand.[14] The general significance of π back-donation is well known. For the present electron-deficient system, the back-donation is of particular significance, for it transmits the electronic charge density into the cationic ligand to counterbalance the developed positive charge. It is expected that the formation of a nonbonding orbital in the cumyl cation[15] upon ionization depresses the energy level of the lowest unoccupied orbital and facilitates back-donation,[15] whereas in the case of the cycloheptatrienylium ion no nonbonding orbital is formed. Consequently the $Cr(CO)_3$ group has less stabilizing effect on the cycloheptatrienylium ion than on the cumyl cation, as also is indicated by the previous pK_R^+ measurements.[7] It is of interest that the ring carbons in **1** which are not at the nodal plane in the nonbonding orbital are more shielded, owing at least in part to the increase of back-donation between these carbons and the metal atom. However, because of the qualitative nature of estimating effects on charge deshielding, the present study *cannot claim to have* detected any transmission of excess charge into the $Cr(CO)_3$ group in **1** due to more favorable π back-donation, by comparison with **2b**.

In addition to the above-mentioned stabilization through back-donation with the interaction of the metal atom with the whole π-electron system of the cationic ligand,[16] the origin[17] of the unusual stabilization of transition metal π complexes containing an exocyclic electron-deficient ligand has been proposed to be due to direct metal participation (**4**),[18] σ–π conjugation (vertical stabilization, **5**),[19] or π–π type overlap.[20] In both chromium tricarbonyl complexed and uncomplexed

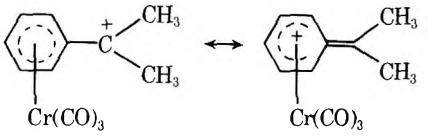
Table III. Carbon-13 Parameters of Cycloheptatriene, Tropylium Ion, and Their π Complexes with Molybdenum, Chromium, and Tungsten Tricarbonyls[a]

Metal carbonyl	Registry no.	C_1	C_2	C_3	C_4	CO	Registry no.	CH	CO
		123.3 (161.1)	129.8 (154)	134.1 (156)	28.8 (131)	*b*		155.33 (168.6)	
$Cr(CO)_3$	12125-72-3	58.15	102.27	100.22	24.17	a 241.34[c,d] b 230.14	12170-19-3	104.71 (179.3)	*e*
$Mo(CO)_3$	12125-77-8	62.36	104.43	99.68	27.08	a 229.17[c,d] b 217.93	12170-21-7	100.0 (176.9)	206.29
$W(CO)_3$	12128-81-3	52.3	101.7	94.2	28.7	211.6 (av)[d]	12083-17-9	96.62 (179.9)	*e*

[a] All chemical shifts (ppm) are referred to the external Me_4Si capillary, and coupling constants (Hz) are given in parentheses. [b] H. Spiesecke and W. G. Schneider, *Tetrahedron Lett.*, 468 (1961); H. Gunther, *Z. Naturforsch.*, 206, 948 (1965). [c] C. G. Kreiter and M. Lang, *J. Organomet. Chem.*, 55, C27 (1973). [d] B. E. Mann, *Chem. Commun.*, 926 (1971). [e] Several attempts were made; however, no resonance was observed for the carbonyl carbons.



4



5

monosubstituted benzene derivatives the ortho and para carbons are generally sensitive to the effect of a ring substituent, whereas the meta carbons are almost unaffected.[3] However, the situation is reversed in **1**. As in the case of arenium–iron tricarbonyl cations,[21] the meta carbons are affected most and become most deshielded. The observation of the reversed deshielding sequence in **1** rules out direct metal participation and π–π type overlap. Although an excellent agreement of the related chemical shifts has been reported between free and chromium tricarbonyl complexed arenes,[3] it cannot be extrapolated to **1**. It indicates that substantial perturbation takes place in the transmission of resonance substituent effects in **1** and rules out the σ–π conjugation. In addition, if **1** would be stabilized by σ–π conjugation, C_i should be observed at a much lower field based on the structures represented as **5**.

Finally, we would like to point out that our estimation of the σ^+ substituent constant of the $Cr(CO)_3$ group and the amount of fractional positive charge transmitted into the metal ligand is clearly qualitative, with the assumption that the shieldings are only moderately affected by the change of bonding nature upon formation of the cations. ^{13}C NMR shift differences clearly cannot be equated with charge delocalization, but qualitatively seem to show their trend.[22] This is considered to be the case also for the cations of transition metal π complexes, although no satisfactory theory is yet available for the shielding effects in these complexes.[23] Furthermore, we also would like to point out that the charge transmission into the $M(CO)_3$ group could be a major contributor to the unusual stabilization. However, it is not the sole factor to be considered and the stabilization is dependent on the charge delocalization of the whole molecule.

Experimental Section

Molybdenum, chromium, and tungsten carbonyls were obtained from Strem Chemicals, Inc. Cycloheptatriene and cumyl alcohol were purchased from the Aldrich Chemical Co. Cycloheptatrienyl–$M(CO)_3$ ions (M = Mo, Cr, and W) were conveniently prepared, as reported, by hydride abstraction from the corresponding cycloheptatriene–$M(CO)_3$ complexes with triphenylcarbenium tetrafluoroborate.[11] Cumyl alcohol–chromium tricarbonyl was prepared as reported.[4] A dark green solution of the cumylchromium tricarbonyl cation was obtained upon treatment of the alcohol in cold $CDCl_3$ with fluorosulfuric acid in SO_2 at −80°, under dry nitrogen. The cation is stable indefinitely up to −30 °C.

The ^1H NMR spectra were obtained on a Varian A56/60A spectrometer with a capillary of Me_4Si as external reference. FT ^{13}C NMR spectra were obtained on a Varian XL-100 spectrometer, using fluorobenzene as external lock. All chemical shifts are referred to the external Me_4Si (5% enriched capillary).

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Friedel–Crafts Alkylations with Vinyl Halides.[1] Vinyl Cations and Spirobiindans

Royston M. Roberts* and Mahmoud B. Abdel-Baset

Department of Chemistry, The University of Texas, Austin, Texas 78712

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Alkylation of toluene with 1-bromo-1-phenylethene (**1**, α-bromostyrene) in the presence of Al_2Br_6 produced 1-phenyl-1-*p*-tolylethene (**4a**) and minor amounts of phenylacetylene (**2**) and acetophenone (**3**). Reaction of **2** with toluene and Al_2Br_6 gave a low yield of 1-phenyl-1-*o*-tolylethene (**4b**) and a trace of **1**. Reaction of **2** with toluene and 100% H_3PO_4 gave **3** (mainly) and **4a** and **4b**. Reaction of **2** with anisole and 100% H_3PO_4 gave 1-phenyl-1-*p*-anisylethene (**4c**), 1-phenyl-1-*o*-anisylethene (**4d**), and **3**. Extended reactions of both **1** and **2** with toluene and anisole give polymeric products; **4c** was shown to polymerize faster than **4d**. The vinyl cation $C_6H_5C^+{=}CH_2$ is a presumed intermediate in these reactions. The major product from the reaction of benzene with 2-bromopropene in the presence of aluminum bromide is 2,2-diphenylpropane (**12a**). Minor products include 3,3,3′,3′-tetramethyl-1,1′-spirobiindan (**21a**), 1,1,3-trimethyl-3-phenylindan (**14a**), and 1,1,3-trimethylindene (**16a**). The corresponding products are formed from toluene. The key intermediates to all of these products are the 2-arylpropene (**10a**) and the 2-aryl-2-propyl cation (**11a**) produced from it by proton addition. Results of the earlier work in which the production of 1,1′-spirobiindans has been observed are correlated in terms of the mechanisms outlined.

1-Bromo-1-phenylethene. Depending on the catalyst and the conditions used, vinyl halides may react either at the double bond or at both the double bond and the halide sites.[2-4] Yuldashev and Tsukervanik[3] found that treatment of vinyl halides in benzene with BF_3–H_3PO_4 gave the corresponding phenylalkyl halides, whereas using $AlCl_3$ gave products resulting from reaction at both the double bond and the halide site. However, they reported that 1-bromo-1-phenylethene (**1**, α-bromostyrene) did not react with benzene in the presence of either $AlCl_3$ or BF_3–H_3PO_4 catalysts. They concluded that substitution of vinyl halides at the α position with alkyl or particularly aryl groups diminishes the reactivity of the double bond in alkylation reactions.

We investigated the reaction of 1-bromo-1-phenylethene (**1**) with toluene in the presence of Al_2Br_6 catalyst with the main interest of examining the possibility of a vinyl cation intermediate. Surprisingly, we found that **1** condensed rapidly with toluene in the presence of Al_2Br_6 to give mainly 1-phenyl-1-*p*-tolylethene (**4a**), besides small amounts of acetophenone (**3**) and phenylacetylene (**2**). The reaction was very fast and **4a** was detected by GLC as the main product after 3 min. At longer reaction times compound **4a** polymerized to higher boiling materials, as will be discussed later.

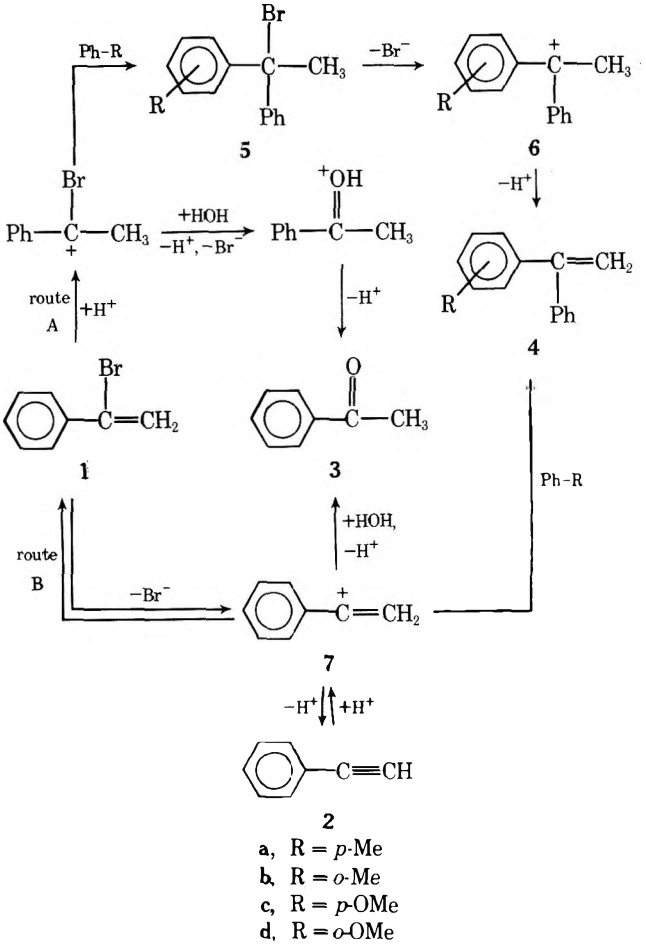
At least two mechanisms may account for these results. The first mechanism (route A of Scheme I) involves reaction at the double bond by addition of a proton or the Lewis acid catalyst to give a fairly stable cation, which either reacts with water to give acetophenone (**3**) or with toluene to give 1-phenyl-1-tolyl-1-bromoethane **5**. Compound **5** was not isolated, but it would be expected to react further in the presence of the catalyst to give a very stable cation (**6**) which then gives **4**. Further alkylation with **6** to give a triarylethane is unlikely owing to steric effects. Even if such alkylation took place, a dealkylation is likely to occur. This latter possibility was ruled out since no compound such as 1,1-ditolylethene was detected among the products.

The second mechanism (route B of Scheme I) involves direct ionization of **1** to a phenylvinyl cation **7** which either reacts with water to give acetophenone (**3**) or with the solvent to give 1-phenyl-1-tolylethene (**4**). Loss of a proton from **7** gives phenylacetylene (**2**).

To gain more insight on the possibility of vinyl cation intermediates in the course of Friedel–Crafts alkylation, the reaction of phenylacetylene with aromatic hydrocarbons in the presence of a protonic catalyst was studied. The catalyzed hydration of substituted phenylacetylenes in aqueous acidic solvents to give substituted acetophenones was shown to involve a rate-determining proton transfer to give arylvinyl cation intermediates.[5,6] This conclusion was supported by a large increase in the rate of the reaction produced by electron-releasing substituents on the benzene ring and a large negative ρ value. A large kinetic isotope effect, k H_2SO_4/k D_2SO_4, of 2.98 for phenylacetylene was obtained, consistent with a rate-determining proton transfer. Phenylacetylene was reported to condense with anisole in the presence of $AlCl_3$ to give (16%) 1-*p*-anisyl-1-phenylethene (**4c**) among other products.[7]

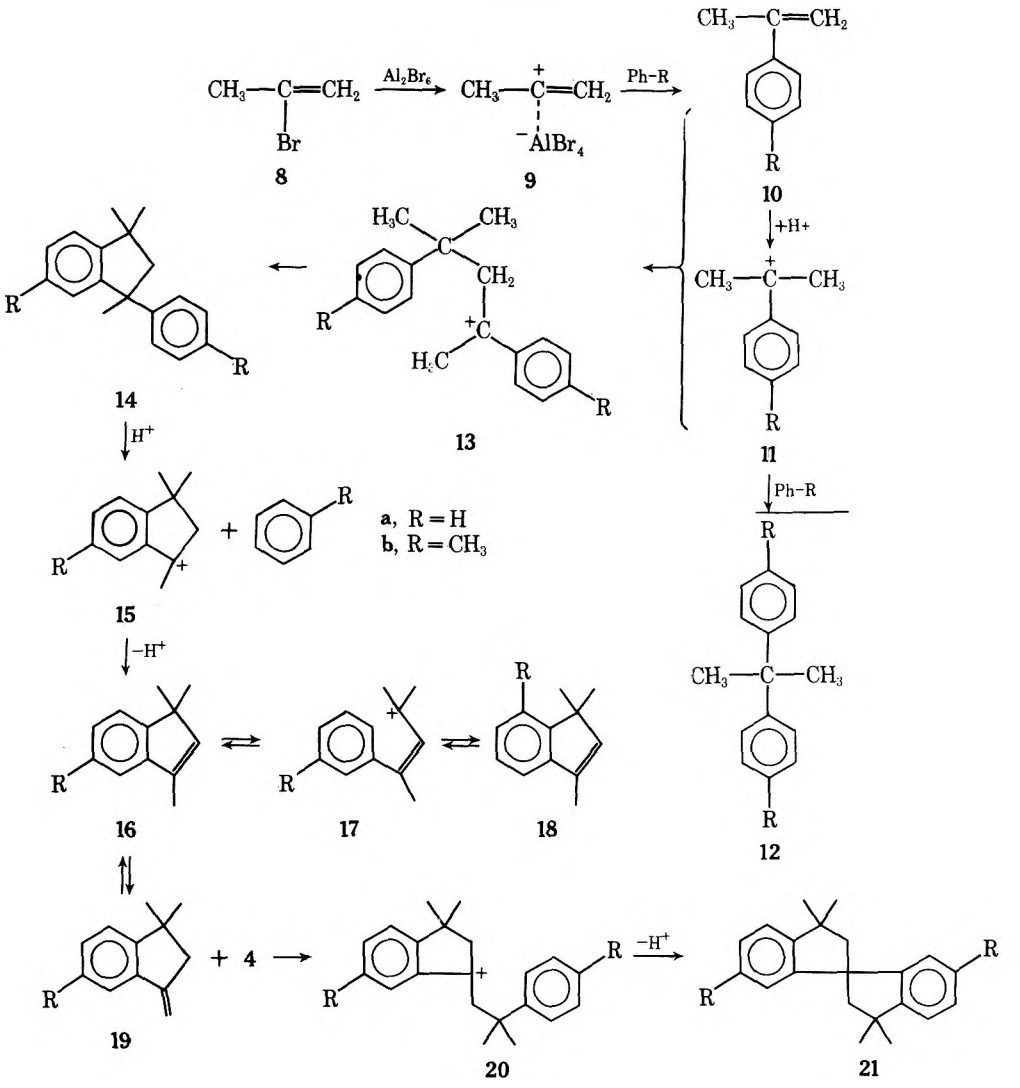
In the presence of BF_3–H_3PO_4, phenylacetylene was reported to condense with toluene to give 1-phenyl-1-tolyleth-

Scheme I



a, R = *p*-Me
b, R = *o*-Me
c, R = *p*-OMe
d, R = *o*-OMe

Scheme II



ene.[8] Phosphoric acid alone was used as catalyst in this investigation because the only way it could catalyze the reaction of phenylacetylene would be through proton addition to the triple bond to produce a vinyl cation. Phenylacetylene reacted with toluene in the presence of H_3PO_4 to produce 40% acetophenone (**3**), 7% 1-phenyl-1-*p*-tolylethene (**4a**), and 5% 1-phenyl-1-*o*-tolylethene (**4b**). Treatment of phenylacetylene with anisole and H_3PO_4 gave 25% acetophenone (**3**), 14% 1-*p*-anisyl-1-phenylethene (**4c**), and 12% 1-*o*-anisyl-1-phenylethene (**4d**). When Al_2Br_6 was used as catalyst in the presence of toluene, 1-bromo-1-phenylethene (**1**) was formed besides **4b**. The fact that **1** reacts with toluene and Al_2Br_6 to give **2** and **4** and that **2** reacts with toluene and Al_2Br_6 to give **1** and **4** suggests that the vinyl cation **7** is a reasonable common intermediate, but it does not necessarily rule out route A as an alternative pathway from **1** to **4**.

In the reaction of phenylacetylene with toluene, the ratio of alkylation to acetophenone formation was 12:40, whereas in the reaction with anisole it was 25:26. This probably reflects the higher reactivity of anisole toward electrophilic attack by the phenylvinyl cation, **7**.

It was surprising to find a high ratio of ortho-alkylation product. We suspected that the para isomers were formed initially in higher ratios, but they then polymerized at higher rates than the ortho isomers. The relative rates of formation and polymerization of both isomers (Table I) show that at the shortest reaction time the para isomer was formed more than twice as fast as the ortho isomer. At longer reaction times the percentage of the para isomer decreased, and after 30 min, almost equal amounts of both isomers were detected. Finally, after about 5 h, both isomers disappeared with the formation of polymeric materials.

The failure of Yuldashev and Tsukervanik[3] to obtain alkylation of benzene with 1-bromo-1-phenylethene may be attributed to two causes, the first of which is polymerization of the initial product, 1,1-diphenylethene. Secondly, the type of products they found from the other vinyl halides and arenes with $AlCl_3$ catalyst—those due to reaction at both the double bond and the halide site—were not formed because of the steric hindrance to introducing three aromatic rings on one carbon atom.

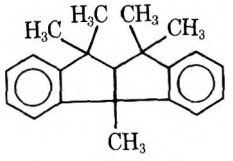
2-Bromopropene. The reactions of 2-bromopropene follow the general behavior of vinyl halides in that the major products are those resulting from reaction of both functional groups (double bond and halide).[3] However, the minor products of the reactions are very interesting and deserving of comment.

The major product of the reaction of 2-bromopropene (**8**) with benzene in the presence of Al_2Br_6 was 2,2-diphenylpropane (**12a**, Scheme II). Minor products were 1,1,3-trimethyl-3-phenylindan (**14a**), 1,1,3-trimethylindene (**16a**), and 3,3,3′,3′-tetramethyl-1,1′-spirobiindan (**21a**). Compound **21a** has a fascinating history. It was first reported by Hoffman[13] as a hydrocarbon of unknown structure from the reaction of 4-methyl-4-phenyl-2-pentanone with anhydrous $ZnCl_2$. The structure **22** was later assigned to the hydrocarbon by Barnes and Beitchman[14] on the basis of their investigations of similar reactions. This formula was accepted as correct for the product

Table I. Relative Concentrations of 1-o-Anisyl-1-phenylethene (4d) and 1-p-Anisyl-1-phenylethene (4c) Produced in the Presence of 100% H_3PO_4

Time, min	4d, wt %	4c, wt %
5	31	69
15	49	51
30	55	45
45	64	36
60	80	20
150	100	
300	Trace	

obtained from treatment of the "saturated dimer of α-methylstyrene" (1,1,3-trimethyl-3-phenylindan, **14a**) with $AlCl_3$ at 100 °C,[15] for the product obtained from methylacetylene and benzene in the presence of $AlCl_3$ and from treatment of α-methylstyrene (**10a**) with $AlCl_3$,[16] and for the product from reaction of cumene with nitrosonium hexafluorophosphate.[17]



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However, in 1962 Curtis and Lewis[18] demonstrated by NMR studies that the product obtained from all of these reactions was indeed the 1,1′-spirobiindan of structure **21a.** Barclay and Chapman[19] came to the same conclusion, and they proposed a mechanism for the formation of **21a** from 1,1,3-trimethylindene (**16a**) and the carbonium ion **11a** corresponding to the last three steps of Scheme II. The mechanism was supported by their demonstration of the production of **21a** from **16a** and α-methylstyrene (**10a**) in sulfuric acid and of two other new polyalkyl-1,1′-spirobiindans by analogous reactions.

Our contribution to the history of the 1,1′-spirobiindan **21a** consists of the first demonstration of its production from 2-bromopropene and benzene. Although it was not isolated in this experiment, 2-phenylpropene (α-methylstyrene, **10a**) is undoubtedly the initial product from these starting materials, and the rest of the steps in the formation of **21a** follow as outlined in Scheme II. 2-*p*-Tolylpropene (**10b**) was observed among the products from 2-bromopropene and toluene in the presence of aluminum chloride (vide infra). The other products (**12a, 14a,** and **16a**) also fit logically into this scheme. The formation of **21a** in each of the reactions reported in ref 15–17 is also reasonably explained in terms of Scheme II. (Methylacetylene and benzene give α-methylstyrene as one product.[16])

The 1,1′-spirobiindan (**21a**) was isolated in crystalline form only after separation from other products by vacuum distillation and preparative gas chromatography. However, in the work-up of the reaction mixture from 2-bromopropene, toluene, and Al_2Br_6, when the excess toluene was removed by distillation, the residue contained a mass of crystals. This was 3,3,6,3′,3′,6′-hexamethyl-1,1′-spirobiindan (**21b**). This compound had also been identified incorrectly earlier[14] as a homologue of **22,** but the correct structure was established at the same time as that of **21a.**[18] As in the reaction with benzene, the major product of the reaction of 2-bromopropene with toluene was the 2,2-diarylpropane, in this case 2,2-di-*p*-tolylpropane (**12b**), and the other corresponding minor products, 1,1,3,5-tetramethyl-3-*p*-tolylindan (**14b**) and 1,1,3,5-tetramethylindene (**16b**) were observed. An additional product was observed which gave a GLC peak very close to that of **16b** and had an NMR spectrum almost identical with that of **16b** except in the aromatic proton region. It is assumed to be 1,1,3,7-tetramethylindene (**18b**), which is formed from **16b** by a facile dealkylation–realkylation via the stable tertiary allylic cation **17b.**

One experiment was carried out using aluminum chloride as catalyst for the reaction of 2-bromopropene with toluene. The major product was 2,2-di-*p*-tolylpropane (**12b**), as with Al_2Br_6 catalyst, and the minor products **14b, 16b,** and **18b** were observed. An interesting difference in the results was the isolation of 2-*p*-tolylpropene, which was not identified among the products of the Al_2Br_6-catalyzed reaction, and the failure to isolate any 1,1′-spirobiindan (**21b**).

Barclay and Chapman[19] commented on the interesting NMR spectrum of **21a** and rationalized it in terms of the space relationships imposed by the rigid spirane structure. We found the NMR spectrum of **21b** also interesting, although it was highly perplexing at first. In CCl_4 solution the spectrum was surprisingly simple, consisting of five sharp singlets (Experimental Section). The two six-proton signals at 1.30 and 1.37 ppm could be assigned to two sets of equivalent methyl groups (at the 3,3′ positions), and the two singlets in the aromatic regions, two protons at 6.49 and four protons at 6.92 ppm, could be assigned in the same way as the corresponding ones in **21a** were assigned by Barclay and Chapman[19] (to the 7,7′ and 4,5,4′,5′ positions), but the ten-proton singlet at 2.24 ppm defied assignment. However, when the NMR spectrum was determined in pyridine solution, the signal at 2.24 ppm was separated into two singlets at 2.16 (6 H, 6,6′-$ArCH_3$'s) and 2.32 ppm (4 H, 2,2′-CH_2's). It was indeed surprising that the methylene hydrogens at the 2 and 2′ positions would give the same signal as the methyl groups at the 6 and 6′ positions in CCl_4 solution.

Experimental Section

Mass spectra were recorded on a Du Pont 21-491 spectrometer. ^1H NMR spectra were obtained using a Varian A-60 or HA-100 spectrometer, or a Perkin-Elmer R-12 spectrometer, in CCl_4 solution unless specified otherwise; results are expressed in parts per million downfield from internal Me_4Si (δ). Ir spectra were recorded on a Beckman IR-5A instrument.

Anhydrous aluminum bromide was prepared from aluminum, 30 mesh (50 g), and bromine (60 ml).[9]

1-Bromo-1-phenylethene (**1**) was prepared according to the procedure of Dufraisse[10] using phenylacetylene (0.147 mol) in glacial acetic acid (100 ml) and hydrogen bromide (0.118 mol) at 0 °C, bp 63 °C (2.5 mm).

Treatment of 1-Bromo-1-phenylethene (1) with Al_2Br_6 in Toluene. Freshly distilled Al_2Br_6 (3.0 g, 5.5 mmol) was dissolved in toluene (20 ml, 200 mmol). 1-Bromo-1-phenylethene (**1,** 3.0 g, 17 mmol) was added slowly during 5 min while stirring at room temperature for 30 min. Heat was evolved and the solution turned red. The usual workup with dilute HCl followed by vacuum distillation gave 1.2 g of an oil, bp 133–150 °C (2.5 mm), which was separated by preparative GLC (10-ft column, 10% SE-30 at 200 °C) and was found to be (4%) phenylacetylene (**2**), (8%) acetophenone (**3**), and (88%) 1-phenyl-1-*p*-tolylethene (**4a**):[11] mass spectrum *m/e* 194; NMR δ 2.28 (s, 3 H, $ArCH_3$), 5.31 (broad singlet, 2 H, C=CH_2, 7.04 (d, 4 H, ArH), and 7.2 ppm (s, 5 H, ArH). The yield of **4a** was 35% based on **1.**

Treatment of Phenylacetylene (2) with Al_2Br_6 in Toluene. Phenylacetylene (**2,** 4.2 g, 41 mmol) was dissolved in toluene (40 ml) and the solution was added dropwise into a cold solution (0 °C) of Al_2Br_6 (0.95 mmol) in toluene (50 ml). The mixture was stirred at 0 °C for 5 h. Regular workup with dilute HCl gave 4 g of a viscous oil. Vacuum distillation gave 0.2 g of an oil, bp 112–140 °C (0.05 mm). The overall yield was estimated to be about 5% of a mixture which was separated by preparative GLC and consisted of (10%) 1-bromo-1-phenylethene (**1**), mass spectrum *m/e* 182 (100%), 183 (13%), and 184 (99%), NMR δ 5.96 (d, 1 H, *J* = 1 Hz), 6.05 (d, 1 H, *J* = 1 Hz), and 7.1–8 ppm (m, 5 H), and (85%) 1-phenyl-1-*o*-tolylethene (**4b**), mass spectrum *m/e* 194, NMR (CS_2) δ 1.99 (s, 3 H, $ArCH_3$), 5.08 (d, 1 H, *J* = 2 Hz, C=CH), 5.65 (d, 1 H, *J* = 2 Hz, C=CH), 7.08 (s, 4 H, ArH), and 7.13 ppm (s, 5 H, ArH).

Treatment of Phenylacetylene (2) in Toluene with H_3PO_4. Anhydrous phosphoric acid was prepared[12] by dissolving 75% of P_2O_5 in 100 g of orthophosphoric acid. The reaction was carried out by

stirring phenylacetylene (**2**, 4.2 g, 41 mmol), toluene (50 ml), and anhydrous H_3PO_4 (10 ml) at 75–80 °C for 8 h. The mixture was worked up with water, extracted with ether, washed with water and 10% Na_2CO_3 solution, and then dried over anhydrous $MgSO_4$. Vacuum distillation gave two fractions: (1) bp 102–103 °C (12 mm), 2 g, and (2) bp 118–125 °C (0.05 mm), 0.4 g. The first fraction was mainly acetophenone (**3**) (40% yield) while the second fraction consisted of a mixture of (5%) 1-phenyl-1-*o*-tolylethene (**4b**) and (7%) 1-phenyl-1-*p*-tolylethene (**4a**).

Treatment of Phenylacetylene (2) in Anisole with H_3PO_4. Phenylacetylene (4.2 g, 41 mmol), anisole (50 ml), and 100% H_3PO_4 (5 ml) were heated at 75–80 °C with vigorous stirring for 9 h. Regular workup as before gave mostly polymeric material with traces of acetophenone (**3**) and 1-anisyl-1-phenylethene. The reaction was repeated, but with only a 30-min reaction period, to give (25%) acetophenone (**3**), (12%) 1-*o*-anisyl-1-phenylethene (**4d**), mass spectrum *m/e* 210, NMR δ 3.56 (s, 3 H, OCH_3), 5.20 (d, 1 H, *J* = 2 Hz, C=CH), 5.58 (d, 1 H, *J* = 2 Hz, CCH), and 6.8–7.16 ppm (singlet with multiplet at base, 9 H, ArH), and (14%) 1-*p*-anisyl-1-phenylethene (**4c**), mp 74–75 °C (ethanol) (lit.[7] 75–76 °C), mass spectrum *m/e* 210, NMR δ 3.70 (s, 3 H, OCH_3), 5.28 (q, AB system, 2 H, CCH_2), 6.6–7.2 (an AA′BB′ system, 4 H, ArH), and 7.22 ppm (s, 5 H, ArH).

Relative Rates of Formation of 1-o-Anisyl-1-phenylethene (4d) and 1-p-Anisyl-1-phenylethene (4c). Phenylacetylene (**2**, 4.2 g, 41 mmol), anisole (50 ml), and 100% H_3PO_4 (5 ml) were heated at 75–80 °C with vigorous stirring; samples were withdrawn at different intervals and worked up as usual, then analyzed by GLC, and the relative concentrations of **4d** and **4c** were calculated from the corresponding peak areas. The GLC column was 5 ft × 0.125 in., 10% SE-30, used at 150 °C with nitrogen at 10 psi. The results are summarized in Table I.

Alkylation of Benzene with 2-Bromopropene. Anhydrous Al_2Br_6 (2 g, 3.8 mmol) was distilled into a 250-ml flask; 90 ml of benzene was added and the mixture was stirred at room temperature until all the Al_2Br_6 was dissolved. 2-Bromopropene (4.5 g, 37 mmol) was added dropwise during 5 min and stirring was continued for 3 h. The usual workup with ice and water followed by distillation under reduced pressure gave 4.2 g of crude product, bp 96 °C (10 mm)–133 °C (1 mm). This mixture was separated by preparative GLC using a Wilkens A-700 (Autoprep) instrument with 6 ft × 0.25 in. column containing 10% SE-30 on 60–80 mesh firebrick, He carrier gas. The approximate composition was 10% 1,1,3-trimethylindene (**16a**),[15] mass spectrum *m/e* 158, NMR (CCl_4) δ 1.25 [s, 6 H, $C_1(CH_3)_2$], 2.05 (broad d, 3 H, C_3CH_3), 5.90 (m, 1 H, $=C_2H$), and 7.10 ppm (s, 4 H, ArH); 78% 2,2-diphenylpropane (**12a**), mass spectrum *m/e* 196, NMR (CCl_4) δ 1.63 [s, 6 H, $C_2(CH_3)_2$] and 7.12 ppm (s, 10 H, ArH); 8% 1,1,3-trimethyl-3-phenylindan (**14a**),[15] mass spectrum *m/e* 236, NMR (CCl_4) δ 1.02 (s, 3 H, C_3CH_3), 1.32 (s, 3 H, C_3CH_3), 1.67 (s, 3 H, C_1CH_3), 2.30 (two d, AB, 2 H, *J* = 13 Hz, C_2H_2), and 7.10 ppm (two s, 9 H, ArH); and 4% 3,3,3′,3′-tetramethyl-1,1′-spirobiindan (**21a**), mp 133–134 °C (from methanol, lit.[13–19] 132, 133–134 °C), mass spectrum *m/e* 276 and 261, NMR (CCl_4) δ 1.35 (s, 6 H, $C_{3,3'}CH_3$), 1.40 (s, 6 H, $C_{3,3'}CH_3$), 2.29 (s, 4 H, $C_{2,2'}H_2$) and 6.9–7.2 ppm (m, 8 H, ArH).

Alkylation of Toluene with 2-Bromopropene. The reaction was carried out as with benzene: Al_2Br_6 (2.1 g, 3.9 mmol), toluene (90 ml), and 2-bromopropene (5 g, 41 mmol) were stirred at room temperature for 4 h. After the usual workup with ice and water and removal of the excess toluene by distillation under reduced pressure, a mass of crystals appeared in the 4.5 g of residual yellow oil. Two recrystallizations of the solid gave 0.5 g of 3,3,6,3′,3′,6′-hexamethyl-1,1′-spirobiindan (**21b**): colorless needles, mp 130–132 °C; vacuum sublimation raised the melting point to 137–138° (lit.[18] 137–138 °C); mass spectrum *m/e* 304 and 289; NMR (CCl_4) δ 1.30 (s, 6 H, $C_{3,3'}CH_3$), 1.37 (s, 6 H, $C_{3,3'}CH_3$), 2.24 (s, 10 H, 6,6′-$ArCH_3$ and 2,2′-CH_2), 6.49 (s, 2 H, 7,7′-ArH), and 6.92 ppm (s, 4 H, 4,5,4′,5′-ArH); (pyridine) δ 2.16 (s, 6 H, 6,6′-$ArCH_3$) and 2.32 ppm (s, 4 H, 2,2′-CH_2). The 0.5 g of pure **21b** corresponds to 12% of theory based on 2-bromopropene.

The liquid products, 3.3 g, bp 68–145 °C (0.1 mm), were separated by preparative GLC, using a 10 ft × 0.25 in. column of the same type described above and the components were identified by NMR: 18% 1,1,3,5-tetramethylindene (**16b**),[20] NMR (CCl_4) δ 1.24 [s, 6 H, $C_1(CH_3)_2$], 2.05 (d, 3 H, *J* = 2 Hz, C_3CH_3), 2.37 (s, 3 H, 5-CH_3), 5.85 (m, 1 H, $=C_2H$), and 6.9–7.1 ppm (m, 3 H, ArH); 4% 1,1,3,7-tetramethylindene (**18b**), NMR (CCl_4) δ 1.22 [s, 6 H, $C_1(CH_3)_2$], 2.25 (d, 3 H, *J* = 2 Hz, C_3CH_3), 2.51 (s, 3 H, 7-CH_3), 5.88 (m, 1 H, $=C_2H$), and 6.8–7.2 ppm (m, 3 H, ArH); 71% 2,2-di-*p*-tolylpropane (**12b**), NMR δ 1.6 [s, 6 H, $C_2(CH_3)_2$], 2.24 (s, 6 H, $ArCH_3$), and 6.97 ppm (s, 8 H, ArH); and 7% 1,3,3,6-tetramethyl-1-*p*-tolylindan (**14b**),[21] NMR (CCl_4) δ 1.02 (s, 3 H, C_3CH_3), 1.30 (s, 3 H, C_3CH_3), 1.62 (s, 3 H, C_1CH_3), 2.28–2.35 (two singlets with multiplet at base, 8 H, C_2H_2 and $ArCH_3$), and 6.95 ppm (m, 7 H, ArH).

Alkylation of Toluene with 2-Bromopropene in the Presence of Anhydrous Aluminum Chloride. 2-Bromopropene (1.95 g, 16 mmol), $AlCl_3$ (2.66 g, 20 mmol), and toluene (90 ml) were stirred together at room temperature for 2.5 h. After the usual workup with ice and water and removal of excess toluene by distillation under reduced pressure, the residue was 2.2 g of yellow oil, which did not yield any crystals. This oil was separated by GLC into the same components (**12b**, **14b**, **16b**, and **18b**) as in the Al_2Br_6-catalyzed reaction except that no 1,1′-spirobiindan (**21b**) was found, and 7% of 2-*p*-tolylpropene (**10b**) was isolated and identified by NMR (CCl_4): δ 2.11 (s with fine splitting, 3 H, $=C_2CH_3$), 2.34 (s, 3 H, $ArCH_3$), 4.98 (broad s, 1 H, C_1H), 5.24 (broad s, 1 H, C_1H), and 7.14 ppm (AB quartet, 4 H, ArH).

Registry No.—**1**, 98-81-7; **2**, 536-74-3; **3**, 98-86-2; **4a**, 948-55-0; **4b**, 947-77-3; **4c**, 4333-75-9; **4d**, 24892-80-6; **8**, 557-93-7; **10b**, 1195-32-0; **12a**, 778-22-3; **12b**, 1823-31-0; **14a**, 3910-35-8; **14b**, 1153-36-2; **16a**, 2177-45-9; **16b**, 14656-06-5; **18b**, 58343-28-5; **21a**, 58343-29-6; **21b**, 58343-30-9; Al_2Br_6, 18898-34-5; H_3PO_4, 7664-38-2; $AlCl_3$, 7446-70-0; toluene, 108-88-3; anisole, 100-66-3; benzene, 71-43-2.

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Photostimulated Arylation of Ketone Enolate Ions by the SRN1 Mechanism[1,2,3]

Joseph F. Bunnett* and John E. Sundberg

University of California, Santa Cruz, California 95064

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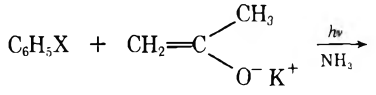
Enolate ions from several open-chain and cyclic ketones react with bromo- or iodobenzene in liquid ammonia, under irradiation, to form α-phenyl derivatives of the ketones. The reaction is of wide scope, but it fails with the enolate ions of acetophenone and of several β-dicarbonyl compounds, and is impeded by appreciable steric hindrance. The lethargic reaction of iodobenzene with the enolate ion of diisopropyl ketone afforded, besides some α-phenyl ketone, nearly equal yields of benzene and of a hexamethyloctanedione; this provides insight into a yield-limiting and rate-depressing side reaction. The dianion of 2,4-pentanedione is mesitylated by 2-bromomesitylene at the terminal carbon in high yield.

In 1972 it was discovered[4] that acetone enolate ion (**1**) reacts readily with unsubstituted phenyl halides in liquid ammonia under photostimulation to form phenylacetone (**2**), accompanied by some 1,1-diphenyl-2-propanone (**3**).



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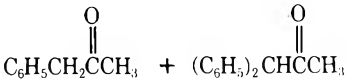


2 **3**

Later it was shown that enolate ions derived from 2-butanone and 3-methyl-2-butanone are similarly phenylated,[5] that acetone enolate ion can be arylated by a great variety of aryl halides,[6] that ketone enolate ions can be 2-quinolinylated by photostimulated reaction with 2-chloroquinoline,[7] and that 1-chloronaphthalene reacts in similar fashion with the enolate ions of acetone and other ketones to form α-(1-naphthyl) derivatives of them.[8]

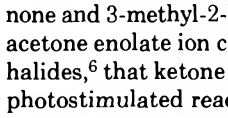
We now report a further study to establish the scope of this synthetic method. We have investigated reactions of bromo- or iodobenzene with enolate ions from diverse ketones, and in a few cases reactions of bromo- or iodomesitylene. The results illuminate aspects of the reaction mechanism, apart from their interest for synthesis.

Results

Reactions were conducted in liquid ammonia at reflux with irradiation through Pyrex from fluorescent lamps emitting maximally at 350 nm. Solutions of ketone enolate ions were prepared by reaction of the ketone with a slight excess of potassium *tert*-butoxide (*t*-BuOK) in ammonia. Except in a few special cases, the ketone enolate ion was in approximately a threefold excess over the aryl halide during irradiation.

The ten experiments summarized in Table I concern reactions with the enolate ions of noncyclic ketones. 3-Pentanone (expt 4) and 4-heptanone (expt 7) are phenylated at α positions in 80% yield, and the yield is even higher for phenylation of 3,3-dimethyl-2-butanone at the 1 position (expt 3). In these cases, the chief interference is by a second stage of phenylation to form diphenyl derivatives of the starting ketones.

2,4-Dimethyl-3-pentanone (expt 5 and 6) furnishes a single enolate ion (**4**) in which the nucleophilic α carbon carries two methyl substituents. The photostimulated phenylation of it is sluggish. Under conditions conducive to complete reaction with other enolate ions, reaction of either bromo- or iodobenzene with **4** was incomplete. Recoveries of unreacted halobenzene were 85 and 48%, respectively. Modest yields of the expected α-phenylation product were obtained in both cases. The most interesting product, however, was 2,4,4,5,5,7-hexamethyloctane-3,6-dione (**5**), which can be



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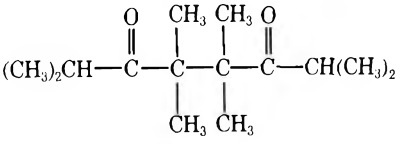

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considered an oxidative dimer of **4**. In expt 6, this was accompanied by a nearly equal yield of benzene, a product of reductive deiodination.

In contrast to these observations, Wolfe and Hay[9] found that the photostimulated reaction of enolate ion **4** with 2-chloroquinoline occurs readily to form an α-arylation product in high yield.

The mesitylation by either bromo- or iodomesitylene of the enolate ions derived from 3-pentanone (expt 9 and 10) is also sluggish. In both cases half or more of the mesityl halide was recovered after reaction times ample for their complete consumption in reaction with acetone enolate ion[6] or for complete reaction of bromobenzene with the enolate ions of 3-pentanone (expt 4). Appreciable amounts of mesitylene were formed in both expt 9 and 10. This suggests a complication analogous to that encountered in expt 5 and 6, but in this case no ketone dimer was obtained as a product.

Phenylation of the enolate ions of methoxyacetone was also lethargic; see expt 8. After 130 min of irradiation, less than 1% of a product that is possibly 1-phenyl-1-methoxy-2-propanone was formed, and 78% of the bromobenzene was recovered. The principal product was phenylacetone, which presumably represents loss of a methoxy group after attachment of phenyl.

Remarkably, the enolate ion of acetophenone is totally unreactive with bromo- or iodobenzene (expt 1 and 2). Even when 10% of acetone enolate ion was also present (an experiment not tabulated), bromobenzene failed to phenylate acetophenone enolate ion. The photostimulated α-naphthylation of acetophenone enolate ion by 1-chloronaphthalene is reported to occur, but very slowly, giving only 8% of α-(1-naphthyl)acetophenone after 3-h irradiation.[8] In contrast, 2-chloroquinoline reacts readily with acetophenone enolate ion under photostimulation to form 2-phenacylquinoline in 82% yield.[7]

Reaction of acetone enolate ion with a threefold excess of bromobenzene (experiment not tabulated) afforded, besides

Table I. Photostimulated Reactions of Phenyl and Mesityl Halides with Enolate Ions of Noncyclic Ketones in Liquid Ammonia

Expt no.	Aryl halide[a]	Ketone	Registry no.	Irradiation time, min	Products[b]
1	PhBr	$PhCOCH_3$	98-86-2	140	PhBr, 99% Br^-, nil
2	PhI	$PhCOCH_3$		180	PhI, 99% I^-, nil
3	PhBr	$CH_3COC(CH_3)_3$	75-97-8	90	$PhCH_2COC(CH_3)_3$, 90% $Ph_2CHCOC(CH_3)_3$, 10% C_6H_6, trace
4	PhBr[c]	$CH_3CH_2COCH_2CH_3$[c]	96-22-0	70	$PhCH(CH_3)COCH_2CH_3$, 80% Diphenyl ketones,[d] 19% C_6H_6, trace
5	PhBr	$(CH_3)_2CHCOCH(CH_3)_2$	565-80-0	90	$PhC(CH_3)_2COCH(CH_3)_2$, 6% C_6H_6, 8% PhBr, 85% Ketone dimer[e,f]
6	PhI	$(CH_3)_2CHCOCH(CH_3)_2$		180	$PhC(CH_3)_2COCH(CH_3)_2$, 32% C_6H_6, 19% PhI, 48% Ketone dimer,[e] 20%[g]
7	PhBr	4-Heptanone	123-19-3	120	$PhCH(C_2H_5)COCH_2CH_2CH_3$, 80% Diphenyl ketones,[h] 10% C_6H_6, 11%
8	PhBr	$CH_3OCH_2COCH_3$	5878-19-3	130	$PhCH(OCH_3)COCH_3$, 0.9% $PhCH_2COCH_3$, 17% PhBr, 78% Br^-, 19%
9	MesBr	$CH_3CH_2COCH_2CH_3$		130	$MesCH(CH_3)COCH_2CH_3$, 14% s-$C_6H_3(CH_3)_3$, 20% MesBr, 58%
10	MesI	$CH_3CH_2COCH_2CH_3$		130	$MesCH(CH_3)COCH_2CH_3$, 24% s-$C_6H_3(CH_3)_3$, 25% MesI, 50%

[a] MesBr is mesityl bromide, etc. [b] Yields by isolation and weighing unless otherwise noted; halide ion yields by titration with $AgNO_3$. [c] Initial concentrations: PhBr, 0.043 M; enolate ions, 0.15 M. [d] Mixture of diphenyl-3-pentanone isomers. [e] 2,4,4,5,5,7-Hexamethyl-3,6-octanedione. [f] Yield not determined. [g] Yield by GLC. [h] Mixture of diphenyl-4-heptanone isomers.

Table II. Photostimulated Reactions of Bromobenzene with Enolate Ions of Cyclic Ketones in Liquid Ammonia

Expt no.	Ketone	Registry no.	Irradiation time, min	Yields,[a] % PhBr	C_6H_6	α-Phenyl ketone	Br^-	Note
11	Cyclobutanone	1191-95-3	150	Tr	4	90	96	
12	Cyclopentanone	120-92-3	150	9	28	64	91	*b*
13	Cyclohexanone	108-94-1	60	18	6	72		
14	Cycloheptanone	502-42-1	210	29	12	58	70	
15	Cyclooctanone	502-49-8	210	0	3	95[c]	100	
16	2-Indanone	615-13-4	150	2	2	90	95	*d*
17	Cyclohex-2-en-1-one	930-68-7	100	92	3	0	8	

[a] Yields by GLC unless otherwise indicated. [b] Bicyclopentyl-2,2′-dione also formed; structure assigned from mass and infrared spectra. [c] Yield 92% by isolation and weighing. [d] Ca. 5% of 2,2′-biindanyl-1,1′-dione also formed; structure assigned from mass spectrum.

32% of phenylacetone (**2**), a 58% yield of 1,1-diphenyl-2-propanone (**3**). None of the symmetrical diphenyl derivative could be detected. Only a trace of a triphenylacetone, of undetermined structure, was found.

Enolate Ions from Cyclic Ketones. The enolate ions of the series cyclobutanone through cyclooctanone were irradiated in the presence of bromobenzene, the enolate ion always being in threefold excess. Results are displayed in Table II, expt 11–15.

A curious pattern emerges, in that the enolate ions of the "even" ketones, cyclobutanone, cyclohexanone, and cyclooctanone, react quite well to form α-phenyl derivatives in high yield, whilst phenylation of the "odd" enolate ions, those from cyclopentanone and cycloheptanone, is less satisfactory. The two "odd" ketones differ, however, in their behavior. The reaction with cyclopentanone enolate ion (expt 12) went nearly to completion but formed a rather large amount (28%) of benzene as well as another by-product which appears to be a ketone dimer, analogous to **5**. The reaction with cycloheptanone enolate ion (expt 14) left 29% of bromobenzene unreacted even after a long irradiation time. Dehalogenation to benzene (12%) was more prominent than with the "even" enolate ions but less than with cyclopentanone enolate ion.

2-Indanone enolate ion (expt 16) was phenylated in high yield. This is similar to the second stage of phenylation of acetone enolate ion, which goes rather well.

The enolate ions of the α,β-unsaturated ketone, cyclohex-2-en-1-one (expt 17), reacted very slowly with bromobenzene. No phenylation product could be found.

Enolate Ions from β-Dicarbonyl Compounds. In experiments not tabulated, but similar in design to those of Tables I and II, efforts were made to phenylate with bromobenzene the monoenolate ions of 2,4-pentanedione, 5,5-dimethyl-1,3-cyclohexanedione, and 1,3-indandione, and with iodobenzene those of diethyl malonate,[10] ethyl acetoacetate,[10] and 2,4-pentanedione. These efforts were all unsuccessful; no phenylation product was obtained (although there was mass spectral evidence of a trace of 3-phenyl-2,4-pentanedione from the iodobenzene reaction), and halide ion release was 12% or less.

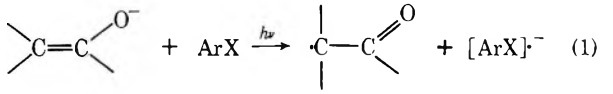
The dianion formed by treatment of 2,4-pentanedione with 2 equiv of KNH_2 was shown by Hauser and co-workers[11] to have high nucleophilic reactivity at the 1 carbon, much greater than at the 3 carbon. Also, the dianion of benzoylacetone was shown to react with 2-chloroquinoline in liquid ammonia preferentially by arylation at the terminal carbon.[12] The SRN1 mechanism was assigned to the latter reaction.

In seeking to determine whether the dianion of 2,4-pentanedione can be arylated by the SRN1 mechanism, we chose 2-bromomesitylene as arylating agent in order to avoid ambiguity as to whether a benzyne mechanism might be involved.[13] The phenylation of this dianion by the benzyne mechanism has been described, but the yield was poor.[11]

In our experiment (not tabulated), the photostimulated reaction of the dipotassium salt of 2,4-pentanedione with 2-bromomesitylene afforded 1-mesityl-2,4-pentanedione in 82% yield, together with 13% of mesitylene. Thus SRN1 arylation at the 1 carbon is very satisfactory.

Discussion

The arylation reactions we have observed are believed to occur by the SRN1 mechanism.[4,14] This mechanism, in schematic form suitable to the present case, is as follows.



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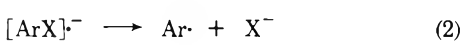

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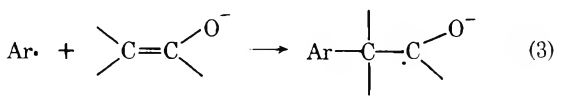

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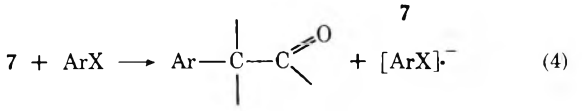


(4)

This is a radical chain mechanism of a type first proposed by Kornblum[15] and Russell[16] and their co-workers for certain substitutions at aliphatic sites. It was recognized as a mechanism of aromatic substitution in 1970.[14]

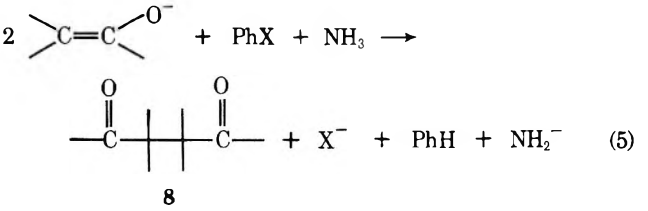
Initiation is represented to occur (step 1) by photostimulated transfer of an electron from the enolate ion to the aryl halide, forming the radical anion of the latter and a β-keto alkyl radical (6). Details of the electron transfer are unclear. A conceivable alternative, photolysis of the C–X bond of the aryl halide,[17] generating an aryl radical which enters the propagation cycle at step 3, is disfavored because iodo- and bromobenzene differ so little in their reactivity with ketone enolate ions.

The $[ArX]\cdot^-$ radical anion ejects halide ion in step 2, and the resulting aryl radical adds, in step 3, to the enolate ion to form species 7, which may be described as a radical anion or a ketyl. It may transfer an electron to another substrate molecule, in step 4, to form an α-aryl ketone and regenerate radical anion $[ArX]\cdot^-$. Steps 2, 3, and 4 constitute the propagation cycle of a chain mechanism. There must also be termination steps, of which we shall have more to say later.

Dehalogenation and Ketone Dimer Formation. Aromatic SRN1 reactions are remarkably insensitive to steric hindrance.[6,13] An example is our observation that the dianion of 2,4-pentanedione is mesitylated by 2-bromomesitylene in 82% yield. However, as the steric requirements of aromatic substituents or of enolate ions increase, both reactivity and yields of arylation products diminish. Thus, in expt 9 and 10, Table I, the mesitylation of 3-pentanone enolate ions is lethargic and the yields of 2-mesityl-3-pentanone produced are rather low. It is to be noted that they are accompanied by larger amounts of mesitylene, a dehalogenation product.

Indeed, inspection of our present results and of others published elsewhere[6] reveals a general tendency for the formation of dehalogenation products to be associated with low overall reactivity. See, for example, expt 5, 6, 12, and 14.

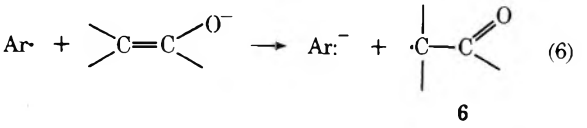
Insight is provided by our discovery of ketone dimer **5** as a by-product of the phenylation of 2,4-dimethyl-3-pentanone enolate ion (**4**) in expt 5 and 6. Significantly, the yield of benzene in expt 6 is equal to that of **5**, consistent with balanced eq 5.



(5)

8

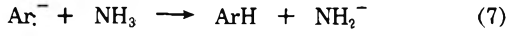
Two mechanisms for the formation of **5** are conceivable. Both involve a second mode of interaction of aryl radical with enolate ion, as in step 6, which parallels step 3. This is an



(6)

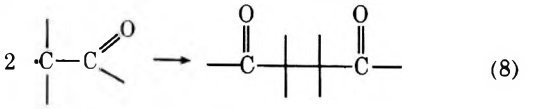
6

electron transfer, and the aryl anion that it forms rapidly takes a proton from the solvent (step 7). The other product of step 6 is β-keto alkyl radical **6**, the same as formed in step 1.



(7)

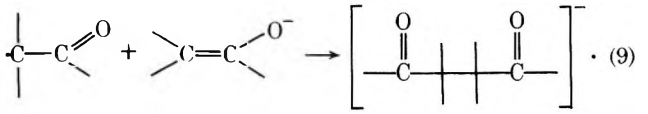
One mode of reaction of β-keto radical **6** is dimerization to ketone dimer **8**, as in step 8. The sum of steps 1, 2, 6, 7, and 8 is eq 5, for which there is experimental support.



(8)

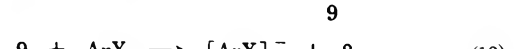
6 8

An alternative possibility is combination of radical **6** with enolate ion, and subsequent electron transfer to a substrate molecule, as in steps 9 and 10. For this alternative, the sum of steps 2, 6, 7, 9, and 10 amounts to eq 5.



(9)

9



(10)

Thus the two alternatives both imply the same stoichiometry. Both are crucially dependent on step 6, for if the aryl radical and enolate ion simply combine as in step 3, radical **6**

is not generated except in relatively small amounts in initiation step 1.

The alternatives differ, however, in one important respect. Step 8 in the set of steps 1, 2, 6, 7, and 8 is a termination step, whereas none of the set of steps 2, 6, 7, 9, and 10 is a termination step. Inasmuch as the formation of dehalogenation products, as well as ketone dimers as in expt 5, 6, 12, and 16, is associated with low overall reactivity, the alternative of steps 1, 2, 6, 7, and 8 is favored.

Dimerization of β-keto alkyl radicals (step 8) is precedented. In point of fact, we synthesized an authentic sample of diketone **5** by just such a reaction.[18]

One would anticipate from the literature that combination of a β-keto alkyl radical with an enolate ion, as in step 9, might well occur. Kornblum, Boyd, and Stuchal[19] present evidence that β-keto alkyl radicals combine in the suggested manner with nitronate ions. Moreover, the cathodic cleavage of 1,4-diketones to form enolate ions, which may involve the reverse of step 9, has been described.[20] Therefore the alternative of steps 2, 6, 7, 9, and 10, although disfavored, cannot be ruled out altogether.

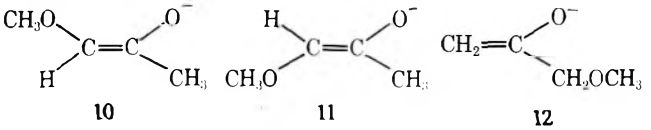
Presuming that we assess the situation correctly, we proceed to ask what determines whether an aryl radical interacts with an enolate ion by covalent bond formation (step 3) or electron transfer (step 6). Steric hindrance has something to do with it, for the formation of dehalogenation products and to some extent of ketone dimers is greater when the aryl radical and/or the enolate ion are cluttered with alkyl substituents. (In some of our experiments ketone dimers, which were not sought as products, may have escaped detection.) However, it is difficult to visualize much steric hindrance in the interaction of phenyl radical with the enolate ion of cyclopentanone (cf. expt 12) or even with **4** (cf. expt 5 and 6). Furthermore, why does the 2-quinolyl radical arylate **4** more rapidly than **1**, seemingly eschewing the electron transfer mode of reaction with **4**?[9] There is much yet to be learned.

Anions from β-Dicarbonyl Compounds. From time to time efforts have been made at Santa Cruz to involve the monoanions of β-dicarbonyl compounds as nucleophiles in aromatic SRN1 reactions.[21] The results have been uniformly unrewarding.

The failure of, for example, the diethyl malonate anion to be arylated by bromobenzene under stimulation either by photons or by solvated electrons[21] might be due to slowness in any of several steps or to high reactivity in competing steps leading to termination. Inasmuch as arylation stimulated by solvated electrons fails, the problem is not primarily in the initiation step. Maybe the anions of β-dicarbonyl compounds are insufficiently nucleophilic to combine fast enough with phenyl radicals (step 3) to maintain the propagation cycle in competition with termination steps. Or maybe they interact primarily by electron transfer, in the manner of step 6, leading to termination.

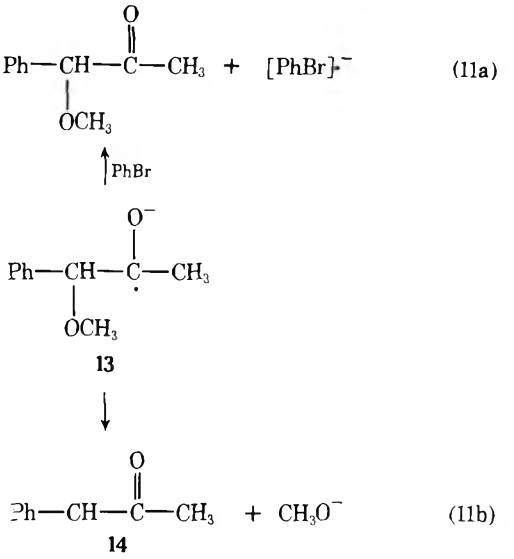
It is noteworthy that numerous instances of *aliphatic* SRN1 reactions involving the anions of β-dicarbonyl compounds as nucleophiles have been recorded by Kornblum and co-workers.[15,22]

Behavior of Methoxyacetone Enolate Ions. Methoxyacetone in principle can form three enolate ions, **10**, **11**, and **12**.



10 **11** **12**

In expt 8, Table I, we obtained at most 0.9% of a product possibly 1-phenyl-1-methoxy-2-propanone, which would derive from **10** and/or **11**; the main product was 17% of phenylacetone (**2**), which probably stems from the same enolate ions. Combination of phenyl radical with **10** or **11** would form **13**. Electron transfer from **13** to bromobenzene (eq 11a)



(11a)

(11b)

would afford 1-phenyl-1-methoxy-2-propanone. However, **13** appears to react preferentially by expulsion of methoxide ion, generating radical **14**. Acquisition of a hydrogen atom by the latter, either directly, perhaps by abstraction from methoxide ion,[23] or indirectly by taking an electron and then a proton, gives **2**, the observed product. Somehow the transformation of **14** to **2** must give rise to radical by-products. If the latter engage mainly in termination, the sluggishness of the overall reaction finds explanation.

The suggested fragmentation of **13** in reaction 11b resembles the fragmentation of phenylacetonitrile radical anion into benzyl radical and cyanide ion.[24]

Experimental Section

General. Reactants were commercial products, sometimes redistilled, whose purity was verified to exceed 99% by GLC analysis. Infrared spectra were recorded on a Perkin-Elmer Model 337 grating spectrophotometer, NMR spectra on a Varian A56/60A or Jeolco Minimar (60 MHz) instrument, and mass spectra on a Hitachi RMU-6E mass spectrometer. Elemental analyses were by Micro-Tech Laboratories, Skokie, Ill. Analytical gas–liquid partition chromatography (GLC) was performed with a Hewlett-Packard Model 5751B chromatograph equipped with flame ionization detector, and product isolation by GLC on a Varian Aerograph A90-P3 instrument with thermal conductivity detector. Columns of either 10% SE-54 silicone rubber or 10% Carbowax 20M on Chromosorb P were used, with helium as carrier gas throughout. Appropriate internal standards were used in analytical GLC work.

Typical Procedure. A three-necked flask (1 l.) was provided with a large cold-finger type condenser (containing solid CO_2 in 2-propanol in its central well) and a nitrogen inlet, and the stoppered third opening was used for additions. The flask was flushed with nitrogen and 240 ml of ammonia was distilled from sodium into it. Magnetic stirring was commenced, and commercial potassium *tert*-butoxide (3.65 g, 0.0325 mol) was added. The mixture was cooled to −70 °C by an external bath of solid CO_2 in 2-propanol, and 2.94 g (0.030 mol) of redistilled cyclohexanone was added. Redistilled bromobenzene (1.57 g, 0.010 mol) was added, and the entire assembly was placed in a Rayonet Model RPR-100 photochemical reactor equipped with 16 "350-nm" lamps and irradiated, with stirring, for 60 min but with interruption every 20 min to wipe accumulated frost from the outside of the flask. The flask was removed from the reactor, excess NH_4NO_3 was added and then 100 ml of diethyl ether, and the ammonia was allowed to evaporate through a condenser of the same type whose central well contained 2-propanol held at about −20 °C by occasional addition of pieces of solid CO_2. (The purpose was to ensure the retention of any benzene formed.) Water was added, the mixture was extracted with ether, and the ether layer was dried over anhydrous $MgSO_4$ and examined by GLC.

In general, if only the anticipated product was indicated to be present, the ether solution was concentrated by evaporation, the

residue was distilled at reduced pressure, and the yield of purified product was determined by weighing. If a mixture was indicated, one or more internal standards was added in weighed amount and yields of the several constituents were determined by GLC; then the ether was removed by evaporation and pure samples of the products were isolated from the residue by preparative GLC. In many cases the aqueous layer remaining after ether extraction was acidified with nitric acid and analyzed for halide ion by potentiometric titration with $AgNO_3$.

Product Identification. Products were identified by their physical properties, and evidence for the main products from the tabulated reactions is now described.

Expt 3. 3,3-Dimethyl-1-phenyl-2-butanone: bp 65–66 °C (0.2 Torr); NMR (CCl_4) δ 1.12 (s, 9), 3.70 (s, 2), 7.23 (s, 5); ir (film) 700, 729, 1060, 1360, 1450, 1475, 1490, 1600, 1710, 2890–3100 cm^{-1}; MS *m/e* 176 (M^+, 10), 91 (98, benzyl?), 85 (100, trimethylacetyl?). **1,1-Diphenyl-3,3-dimethyl-2-butanone:** mp 123–126 °C; NMR (CCl_4) δ 1.12 (s, 9), 5.46 (s, 1), 7.17 (s, 10); MS *m/e* 252 (M^+, 10), 167 (100, benzhydryl?), 152 (biphenylene?), 85 (27, trimethylacetyl?), 57 (30, *tert*-butyl?).

Expt 4. 2-Phenyl-3-pentanone: bp 92–94 °C (4.0 Torr); NMR (CCl_4) δ 0.90 (t, 3), 1.33 (d, 3), 2.29 (q, 2), 3.68 (q, 1), 7.19 (s, 5); this agrees with NMR data reported by Gough et al.[25]

Expt 5 and 6. 2,4-Dimethyl-2-phenyl-3-pentanone: MS *m/e* 190 (M^+, 10), 147 (12, phenyldimethylacetyl?), 119 (100, cumyl?), 77 (80, phenyl?), 71 (dimethylacetyl?); ir (film) 704, 748, 992, 1032, 1350, 1370, 1450, 1703, 2880–3100 cm^{-1}. **2,4,4,5,5,7-Hexamethyl-3,6-octanedione:** NMR (CCl_4) δ 0.83 (d, 12), 1.03 (s, 12), 3.03 (m, 2); ir (film) 992, 1018, 1088, 1380, 1460, 1700, 2850–3000 cm^{-1}, identical with that of an authentic specimen prepared after Ansell et al.[18]

Expt 7. 3-Phenyl-4-heptanone: bp 77–81 °C (0.08 Torr); NMR (CCl_4) δ 0.76 and 0.79 (overlapping triplets, 6), 1.15–2.15 (several small peaks, 4), 2.26 (t, 2, J = 6.2 Hz), 3.44 (t, 1, J = 7.0 Hz), 7.22 (s, 5); ir (film) 701, 757, 1020, 1130, 1350, 1370, 1450, 1490, 1600, 1710, 2880–3100 cm^{-1}; MS *m/e* 190 (M^+, 100), 119 (85, phenylpropyl?), 91 (benzyl?), 71 (butyryl?), 69.5 (metastable, attributed to *m/e* 119 → 91[26]).

Expt 8. Phenylacetone was identified by the match of its NMR spectrum with that of an authentic specimen. The MS of the material responsible for a minor GLC peak of relatively long retention time indicated the presence of some 1-methoxy-1-phenyl-2-propanone (*m/e* 164) and substantial contamination by phenylacetone (*m/e* 134).

Expt 9 and 10. 2-Mesityl-3-pentanone: NMR (CCl_4) δ 0.83 (t, 3, J = 7.5 Hz, H-5), 1.20 (d, 3, J = 7.5, H-1), 2.02 (q, 2, H-4) overlapped by 2.06 (s, 9, aryl CH_3's), 3.63 (q, 1, H-2), 6.57 (s, 2, aryl H); ir (film) 848, 1050, 1450, 1708, 2885–3000 cm^{-1}; MS *m/e* 204 (M^+, 10), 147 (100, mesitylethyl?), 91 (7, benzyl?), 57 (7, propionyl?). Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 81.96; H, 9.93.

Expt 11. 2-Phenylcyclobutanone. The ir spectrum agreed with that reported by Crandall and Conover.[27]

Expt 12. 2-Phenylcyclopentanone: ir absorption at 1740 cm^{-1} was observed, in agreement with Mislow and Hamermesh;[28] MS *m/e* 160 (M^+, 33), 117 (10, cinnamyl?), 104 (100, styrene?), 91 (12, benzyl?), 78 (10, benzene?), 77 (9, phenyl?), 58.5 (metastable, attributed to *m/e* 104 → 78[26]).

Expt 13. 2-Phenylcyclohexanone. The ir spectrum matched the published spectrum.[29a]

Expt 14. 2-Phenylcycloheptanone. The ir spectrum matched the published spectrum.[29b]

Expt 15. 2-Phenylcyclooctanone: bp 115–120 °C (0.4 Torr); NMR (CCl_4) δ 1.4–2.7 (m, 12), 3.64 and 3.83 (two doublets, 1), 7.33 (s, 5); ir (film) 700, 732, 744, 844, 1154, 1190, 1330, 1445, 1490, 1700, 2870–3100 cm^{-1}. The two NMR doublets and the 1700-cm^{-1} ir carbonyl signal agree with a report by Sisti.[30] MS *m/e* 202 (M^+, 17), 117 (87, cinnamyl?), 104 (100, styrene?), 98 (58, cyclohexanone?), 91 (77, benzyl?).

Expt 16. 1-Phenyl-2-indanone. The ir spectrum agreed with that reported by Bordwell and Scamehorn.[31] MS *m/e* 208 (M^+, 61), 178 (100, phenylbenzocyclobutadiene?), 165 (56, phenylbenzocyclopropenyl?), 152 (19, biphenylene?), 115 (13, indenyl?), 104 (47, styrene?).

Reaction of Potassium Acetone Enolate with Excess Bromobenzene. The reaction was conducted in the usual way except that bromobenzene (0.15 M) was in excess over the enolate reagent (0.05 M). Irradiation was for 120 min. Obtained were phenylacetone (32%, by GLC) and 1,1-diphenyl-2-propanone (58%, isolated and weighed). The ir spectrum of the latter matched the published spectrum.[29c]

Reaction of the Dianion of 2,4-Pentanedione with 2-Bromomesitylene. Into about 200 ml of liquid ammonia, 2.35 g (0.06 mol) of potassium metal was introduced and then a little powdered ferric nitrate. After the blue color had disappeared, 3.00 g (0.030 mol) of 2,4-pentanedione was added with stirring, and then 1.99 g (0.010 mol) of 2-bromomesitylene. The mixture was irradiated for 120 min in the photochemical reactor. The product, 1-mesityl-2,4-pentanedione, was isolated by standard procedures: bp 100–105 °C (0.3 Torr); mp 43.5–45 °C; NMR (CCl_4) δ 1.86 (s, 3), 2.16 (s, 9), 3.47 (s, 2), 5.01 (s, 2), 6.67 (s, 2); ir (film) 780, 853, 1234, 1440, 1610, 1705, 2870–3030 cm^{-1}; MS *m/e* 218 (M^+, 60), 200 (40), 160 (50), 141 (35), 134 (98), 133 (100), 119 (80). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.95; H, 8.42.

Registry No.—**1**, 25088-58-8; **5**, 51513-36-1; bromobenzene, 108-86-1; iodobenzene, 591-50-4; mesityl bromide, 576-83-0; mesityl iodide, 4028-63-1; 3,3-dimethyl-1-phenyl-2-butanone, 6721-67-1; 1,1-diphenyl-3,3-dimethyl-2-butanone, 58343-20-7; 2-phenyl-3-pentanone, 16819-77-5; 2,4-dimethyl-2-phenyl-3-pentanone, 25097-60-3; 3-phenyl-4-heptanone, 58343-21-8; 2-mesityl-3-pentanone, 58343-22-9; 2-phenylcyclopentanone, 1198-34-1; 2-phenylcyclooctanone, 14996-79-3; 1-phenyl-2-indanone, 24017-08-1.

References and Notes

(1) Research supported in part by the National Science Foundation.
(2) Based in part on the Dissertation of J. E. Sundberg, University of California, Santa Cruz, June 1975.
(3) Presented in part at the 169th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1975.
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SRN1 Reactions of Vinyl Halides with Thiophenoxide and Acetone Enolate Ions[1]

Joseph F. Bunnett,* Xavier Creary, and John E. Sundberg

University of California, Santa Cruz, California 95064

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Several vinyl halides undergo photostimulated reaction with acetone enolate ion or thiophenoxide ion in liquid ammonia to give substitution products. Although reactivity in some cases is fairly high, in general it is less than for aryl halides. Reactions with thiophenoxide ion are notably sluggish. β-Bromostyrene reacts with the enolate reagent with stimulation by potassium metal to form products of substitution and reduction. These reactions are believed to occur by the SRN1 mechanism.

Although aryl halides without strongly electron-attracting substituents are often thought to be unreactive with nucleophiles, they do react with several under stimulation by electrons or photons to form good yields of substitution products.[2] Prominent examples are the reactions of phenyl halides and similar substrates with amide ion[3,4] or acetone enolate ion,[5] provoked by solvated electrons in ammonia, and the photostimulated reactions of aryl iodides with arenethiolate,[6] dialkyl phosphite,[7] and ketone enolate ions.[8]

These reactions are believed to occur by the SRN1 mechanism. This is a radical chain mechanism, first formulated for certain nucleophilic substitutions at saturated carbon in 1966,[9,10] and recognized for substitutions at aromatic sites in 1970.[3] The propagation steps of the SRN1 mechanism are presented in Scheme I.

Scheme I

$$[RX]\cdot^- \rightarrow R\cdot + X^- \quad (1)$$

$$R\cdot + Y^- \rightarrow [RY]\cdot^- \quad (2)$$

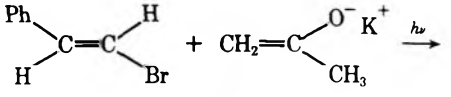
$$[RY]\cdot^- + RX \rightarrow RY + [RX]\cdot^- \quad (3)$$

Initiation may occur by RX accepting an electron (e.g., a solvated electron) to form its radical anion which then breaks up as in step 1. For photostimulated reactions, one possibility is photostimulated electron transfer from nucleophile Y^- to substrate RX, again to form $[RX]\cdot^-$ which enters the propagation cycle at step 1. Another is photolysis of a C–X bond to generate radical R· which enters the cycle at step 2. There must also be termination steps.

Vinyl halides resemble aryl halides in many respects. We now describe an inquiry into SRN1 reactions of vinyl halides.

Results

β-Bromostyrene with Acetone Enolate Ion. A solution of β-bromostyrene (1) and potassium acetone enolate in liquid ammonia in a Pyrex flask was exposed to "350-nm" radiation for 5 h. The main products were one of straightforward substitution, **2**, in 48% yield, and a tautomer thereof, **3**, in 34% yield. There was also 7% of styrene and 3% of unreacted **1**.



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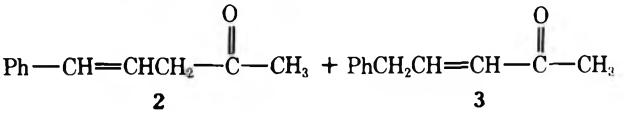
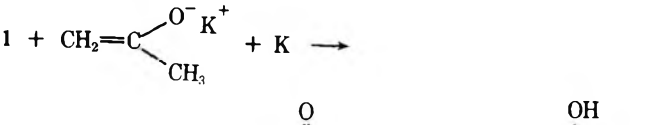


2 **3**

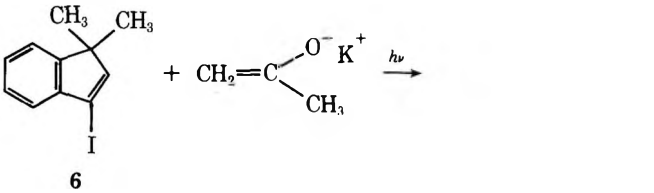
The same reactants were again combined in liquid ammonia and little bits of potassium metal were added one by one. The products obtained had the same carbon skeleton as from the photostimulated reaction but represent lower stages of oxidation. They are the saturated ketone, **4**, in 63% yield and the



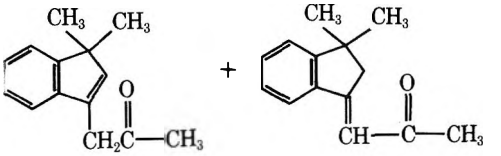
4 **5**

corresponding secondary alcohol, **5**, in 15% yield. Also formed was 6% of styrene.

Reactions of 3,3-Dimethyl-1-iodoindene (6). This substance reacted with acetone enolate ion in liquid ammonia under irradiation for 75 min to form mainly **7**, representing forthright substitution, but also some of **8**, a tautomer of **7**; the total yield was 66%.

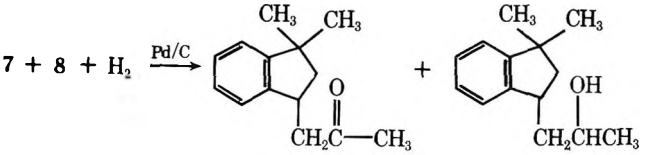


6



7 **8**

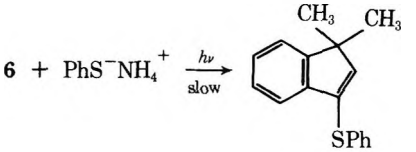
The mixture of **7** and **8** was subjected to catalytic hydrogenation, which afforded saturated ketone **9** and a little of the corresponding alcohol, **10**.



9 **10**

There was no detectable formation of **7** or **8** during 1 h exposure of **6** to excess potassium acetone enolate in liquid ammonia *in the dark*.

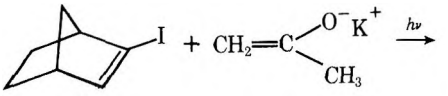
A solution of **6** with excess thiophenol in liquid ammonia was irradiated for 90 min. GLC analysis of the resulting mixture revealed a great deal of unreacted **6**, some diphenyl disulfide, and a new substance, in ca. 20% yield, with mass and infrared spectra consistent with sulfide **11**.



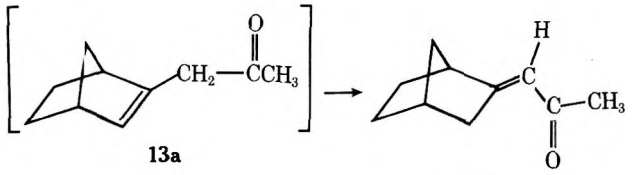
11

Reactions of 2-Iodo-2-norbornene (12). This compound[11] was synthesized by reaction of the hydrazone of 2-norbornanone with iodine and triethylamine,[12] and then with potassium *tert*-butoxide (*t*-BuOK) in *tert*-butyl alcohol (*t*-BuOH). The NMR spectrum indicated that it was free of 1-iodo-2-norbornene. In contrast, the reaction of camphor hydrazone with iodine and triethylamine forms 1-iodocamphene as the major product and only minor amounts of 2-iodo-2-bornene.[12,13] In our system, which lacks methyl substituents, Wagner–Meerwein rearrangement leading to the bridgehead iodide is not a complicating factor. The mechanism of the reaction of camphor hydrazone has been discussed by Pross and Sternhell.[12]

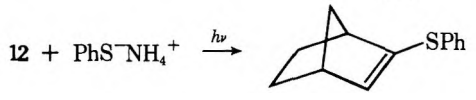
Vinyl iodide **12** reacted rather slowly with acetone enolate ion. In one experiment, only 57% of iodide ion was released during 75-min irradiation. From another, 54% of α,β-unsaturated ketone **13b** was isolated after irradiation for 150 min. This product was doubtless formed via isomer **13a**, probably by base-catalyzed prototropic rearrangement. The position of the double bond in **13b** was established by ozonolysis to 2-norbornanone. Catalytic hydrogenation of **13b** afforded 2-norbornylacetone.



12



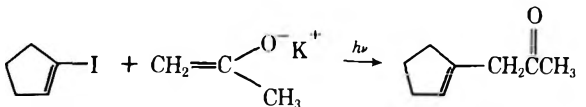
13a **13b**



14

During 2-h irradiation, **12** reacted with excess ammonium thiophenoxide in liquid ammonia to form 22% of substitution product **14**. Diphenyl disulfide was also produced, and much **12** was recovered.

Reactions of 1-Iodocyclopentene (15). This vinyl iodide reacted with acetone enolate ion during 1-h irradiation to release 72% of iodide ion and to form a single product, namely **16**, representing straightforward substitution. In the course



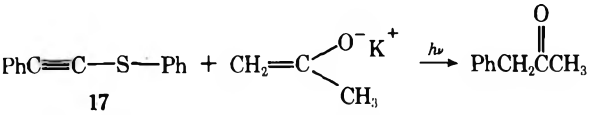
15 **16**

of chromatography on basic alumina, **16** was transformed in part to its α,β-unsaturated isomer.

There was no detectable reaction of **15** with acetone enolate ion in liquid ammonia during 1 h in the dark

Irradiation of a solution of **15** with a twofold excess of potassium diethyl phosphite in ammonia for 80 min caused the release of only 21% of iodide ion. Organic products were not sought.

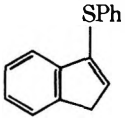
Reaction of Phenyl Phenylethynyl Sulfide (17) with Acetone Enolate Ion. This reaction, during 70 min of irradiation, furnished phenylacetone as the sole ketonic product, in 70% yield. About 15% of **17** remained unreacted. The formation of phenylacetone suggests that reaction occurred with rupture of the phenyl–sulfur bond, in resemblance to the reaction of diphenyl sulfide with acetone enolate ion.[8]



17

Miscellaneous Experiments. During 90-min irradiation, phenyliodoacetylene reacted with ammonium thiophenoxide to form a small amount of **17** and a great deal of phenylacetylene and diphenyl disulfide, and to release iodide ion quantitatively. A dark reaction of the same duration produced 98% of iodide ion as well as high yields of phenylacetylene and diphenyl disulfide,[14] but no **17**. The formation of some **17** under the influence of light is therefore to be attributed to a photochemical reaction in competition with a "dark" reaction.

Treatment of the hydrazone of 1-indanone with iodine and triethylamine afforded a mixture of 1- and 3-iodoindenes, chiefly the latter. The mixture of these two isomers was combined with excess ammonium thiophenoxide in ammonia and submitted to irradiation for 1 h. 1-Indenyl phenyl sulfide (**18**) was produced in about 35% yield, about 15% of the



18

starting iodoindenes was recovered, and much red, probably polymeric material was formed. Inasmuch as we saw indications that 1- and 3-iodoindene interconvert in basic systems (specifically, during chromatography on neutral alumina), and inasmuch as 3-iodoindene is an allylic halide, we cannot exclude the possibility that **18** resulted from an SN2 reaction of thiophenoxide ion with 3-iodoindene and subsequent isomerization of the allylic sulfide.

Discussion

Our experiments show that vinyl halides do react with nucleophiles, under stimulation by photons or electrons, in a fashion similar to aryl halides. Although in some cases reactivity approached that of aryl halides, e.g., in the reactions of **6** and **15** with acetone enolate ion, it was on the whole lower. The lower reactivity of vinyl halides was most pronounced in the reactions with thiophenoxide ion.

In two cases we have shown that reactions that occur under irradiation fail in the dark. Susceptibility to photostimulation is characteristic of many reactions believed to occur by the SRN1 mechanism but is not compelling evidence for it. Although we did not obtain other evidence to support this mechanism, we believe by analogy with reactions of aryl halides that it is also applicable to the vinyl halide reactions of the present study.

The SRN1 mechanism is a radical chain mechanism with many steps. For reactivity to be high, the initiation rate must be adequate and each of the propagation steps must be rapid in respect to termination steps. Our work does not indicate which component of the mechanism is frequently less satisfactory for vinyl halides or why some vinyl halide reactions go better than others.

Experimental Section

General Procedure. Reactions were conducted in liquid ammonia in Pyrex flasks with irradiation in a Rayonet Model RPR-100 photochemical reactor equipped with 16 RPR-3500A lamps rated to emit maximally at 350 nm. The method is described elsewhere.[6,15] Products were isolated and identified by standard procedures.

Preparation of Vinyl Iodides. The method of Pross and Sternhell,[12] involving treatment of a ketone hydrazone with iodine and triethylamine, was used in all cases. Often the initial product appeared to be a mixture of vinyl iodide and *gem*-diiodide, as they reported, and it was therefore treated with *t*-BuOK in refluxing *t*-BuOH to effect elimination of HI from the *gem*-diiodide. The preparation of

1-iodocyclopentene (15) required *t*-BuOK treatment; the product gave an NMR spectrum in agreement with that reported.[12]

The preparation of **3,3-dimethyl-1-iodoindene** (6) from the hydrazone of 3,3-dimethyl-1-indanone also required after-treatment with *t*-BuOK in *t*-BuOH. From 7.0 g of the hydrazone, 12.6 g of crude vinyl iodide was obtained and GLC indicated contamination by the ketone. Chromatography on alumina with elution by pentane, followed by distillation [bp 63–65 °C (0.08 Torr)], afforded 8.3 g of purified **6**: NMR (CCl_4) δ 1.28 (s, CH_3's), 6.65 (s, vinyl H), 7.17 (singlet with broad base, aryl H).

From 10.5 g of the hydrazone of 2-norbornanone, and with after-treatment with *t*-BuOK in *t*-BuOH, there was obtained similarly 7.29 g of **2-iodo-2-norbornene** (12): bp 53–55 °C (4 Torr); NMR (CCl_4) δ 0.83–1.28 (m), 1.28–1.83 (m), 2.66–2.86 (m, H-4), 2.86–3.02 (m, H-1), 6.30 (d, J = 3.0, H-3). The NMR resembles that reported[16] for 2-methoxy-2-norbornene, except that for **12** the signal for H-3 is much farther downfield.

Photostimulated Reaction of β-Bromostyrene (1) with Potassium Acetone Enolate. The enolate was in threefold excess, and irradiation was for 5 h. The ir and NMR spectra of **2** and **3**, isolated by preparative GLC, agreed within experimental error with those reported elsewhere.[17]

Potassium-Stimulated Reaction of β-Bromostyrene (1) with Potassium Acetone Enolate. The general procedure of Rossi and Bunnett[18] was followed, with the enolate in threefold excess over **1**; nearly as many moles of potassium metal as of enolate were used. Products **4** and **5** were recognized by ir and MS. The MS for **4** agrees with the published spectrum.[19]

Reaction of 3,3-Dimethyl-1-iodoindene (6) with Potassium Acetone Enolate. The enolate was in fivefold excess over **6**. The latter was at first an insoluble solid, but at termination of illumination the mixture was homogeneous and red. Products **7** (major) and **8** (minor) were substantially separated by distillation at reduced pressure, and pure samples were obtained by preparative GLC. They were characterized in part by MS: for both *m/e* 200 (M^+), 185, 157, 142, 129, 115, 43. Structures were assigned on the basis of ir: for **7**, $\nu_{C=O}$ 1713 cm^{-1}; for **8**, $\nu_{C=O}$ 1678, $\nu_{C=C}$ 1602 cm^{-1}. NMR (sample stored in glass one year and then redistilled, in CCl_4) δ 1.32 (s, CH_3's), 2.25 (s, CH_3CO), 3.19 (d, $J \approx 2.6$ Hz, CH_2), 6.79 (t, J = 2.6 Hz, vinyl H), 7.25–7.80 (m, aryl H).

Hydrogenation of a portion of the original mixture of **7** and **8** in CH_3OH over 10% palladium on charcoal at 65 psi for 4 h afforded a mixture of **9** (major product) and **10** (minor). Samples of each were isolated by preparative GLC. 1-(3′,3′-Dimethyl-1′-indanyl)-2-propanone (**9**): MS *m/e* 202 (M^+), 187, 165, 129, 43; ir $\nu_{C=O}$ 1720 cm^{-1}; NMR (CCl_4) δ 1.18 (s, CH_3), 1.32 (s, CH_3), 1.2–1.6 (m, ring CH_2), 2.10 (s, $COCH_3$), 2.15–2.85 (m, $-CH_2CO-$), 3.3–3.9 (m, H-1′), 7.02 (s, aryl H). 1-(3′,3′-Dimethyl-1′-indanyl)-2-propanol (**10**): MS *m/e* 204 (M^+), 186, 171, 145, 143, 131, 129; ir ν_{O-H} 3379 cm^{-1}.

Reaction of 6 with Ammonium Thiophenoxide. Thiophenol (2.1 g, 0.019 mol) and **6** (1.69 g, 0.00626 mol) in 150 ml of ammonia were irradiated for 90 min GLC analysis indicated much unreacted **6**, some diphenyl disulfide, and about 20% of phenyl 3,3-dimethyl-1-indenyl sulfide (**11**), isolated by preparative GLC: MS *m/e* 252 (M^+), 237, 221, 202, 143; ir 686, 740, 750, 1020, 1275, 1440, 1450, 1465, 1480, 1550, 1585, 1605, 2855, 2915, and 2958 cm^{-1}.

Reaction of 2-Iodo-2-norbornene (12) with Potassium Acetone Enolate. The enolate was in fourfold excess over **12**. 1-(2′-Norbornylidene)-2-propanone (**13b**) was isolated by distillation at reduced pressure and then preparative GLC on an SE-54 silicone column at 120 °C: MS *m/e* 150 (M^+), 135, 122, 107, 91, 79; ir $\nu_{C=O}$ and $\nu_{C=C}$ complex with absorption at 1623, 1663, and 1691 cm^{-1}; NMR (CCl_4) δ 1.0–1.8 (complex series), 2.07 (s, CH_3), 2.48 (broad singlet, 3′-CH_2), 2.68–2.85 (broad, H-1 and H-4), 6.17 (m, H-1). The stereoisomer of **13b** isolated is tentatively recognized as the *E* isomer, with acetyl trans to the 1′ bridgehead, on the basis of NMR spectral characteristics in comparison with those of related compounds currently under investigation.[20]

A sample (300 mg) of ketone **13b** was dissolved in 10 ml of methanol and ozone was passed through at −78 °C until a blue tint was evident in the solution. To the mixture, after it had warmed to room temperature, a solution of 2 g of NaI in water was added, and then diethyl ether. The ether layer was separated, washed with sodium thiosulfate solution, water, and saturated aqueous NaCl, and dried over anhydrous Na_2SO_4. The ether was removed and the residue distilled through a Vigreux column. The distillate (0.111 g, 50%) gave a single GLC peak; the GLC retention time and the infrared spectrum were identical with those of an authentic sample of 2-norbornanone.

Catalytic hydrogenation of **13** (in CH_3OH over 10% Pd/C) afforded 1-(2′-norbornyl)-2-propanone: MS *m/e* 152 (M^+), 137, 134, 109, 94, 67, 43; ir $\nu_{C=O}$ 1718 cm^{-1}; NMR ($CDCl_3$) δ 1.0–2.55 (m, peaking at 1.37), 2.18 (s, CH_3), 2.48 (broad singlet, $-CH_2CO-$). Which stereoisomer(s) was obtained is not defined.

Reaction of 12 with Ammonium Thiophenoxide. Thiophenol was provided in threefold excess over **12**. Phenyl 2-norbornenyl sulfide (**14**) was separated for the most part from unreacted **12** by distillation at reduced pressure, and an analytical sample was isolated by preparative GLC on an SE-54 silicone column: MS *m/e* 202 (M^+), 174 (there were also peaks at *m/e* 218, appropriate for the diphenyl disulfide molecule ion, as well as a very small one at *m/e* 312, appropriate for the molecule ion of an adduct of thiophenol to **14**); NMR (CCl_4) δ 1.02 (br), 1.17 (br), 1.40 (t, J = 2.0 Hz), 1.53 (d, J = 2.5 Hz), 1.69 (d, J = 2.0 Hz), 2.74 (br), 2.87 (br), 5.87 (d, J = 3.0 Hz), 7.20 (m), resembling those reported for 2-norbornene[21] and 2-methoxy-2-norbornene;[16] ir 685, 735, 1020, 1303, 1440, 1478, 1583, 2865, 2945, and 2960 cm^{-1}.

Reaction of 1-Iodocyclopentene (15) with Potassium Acetone Enolate. The enolate was in 4.5-fold excess over **15**. 1-(1′-Cyclopentenyl)-2-propanone (**16**) was isolated by preparative GLC on an SE-54 silicone column at 100 °C: ir $\nu_{C=O}$ 1712 cm^{-1}; MS *m/e* 124 (M^+), 109, 81, 67, 53, 43. Formed from **16** in the course of chromatography on alumina and isolated by GLC as above was 1-cyclopentylidene-2-propanone: ir[22] $\nu_{C=O}$ 1691, $\nu_{C=C}$ 1612 cm^{-1}; MS *m/e* 124 (M^+), 109, 81, 67, 66, 53, 43.

Reaction of Phenyl Phenylethynyl Sulfide (17) with Potassium Acetone Enolate. Authentic **17** was prepared by the method of Truce, Hill, and Boudakian.[23] The enolate ion was in fourfold excess over **17**. Phenylacetone was recognized by GLC retention time analysis and determined by GLC with naphthalene as internal standard.

Reactions Leading to 1-Indenyl Phenyl Sulfide (18). Reaction of 1-indanone hydrazone with iodine and triethylamine in tetrahydrofuran[12] afforded a product mixture purified by liquid chromatography on neutral alumina with pentane eluent. NMR showed the mixture to comprise mainly 3-iodoindene: δ 5.72 (m, H-3), 6.35 (d of d, J = 5.5, 2 Hz, H-2), 6.60 (d, J = 5.5 Hz, H-1). The minor component, of longer retention time, was 1-iodoindene: NMR δ 3.23 (d, J = 2 Hz, 2 H, H-1), 6.73 (t, J = 2 Hz, 1 H, H-2). Reaction of this mixture with ammonium thiophenoxide gave a product mixture from which **18** was isolated in ca. 35% yield by liquid chromatography on basic alumina with pentane eluent. For **18**: MS *m/e* 224 (M^+), 147, 115 (plus a small contaminant, maybe the sulfoxide, at *m/e* 240, 131); NMR (CCl_4) δ 3.30 (d, J = 2 Hz, 2 H, H-3), 6.37 (t, J = 2 Hz, 1 H, H-2), 7.16 (br m, 4 H, aromatic); ir (film) 683, 710, 735, 757, 1435, 1475, 1580, 2870, 3000, and 3050 cm^{-1}.

Registry No.—**1**, 103-64-0; **6**, 58426-10-1; **7**, 58426-11-2; **9**, 58426-12-3; **10**, 58426-13-4; **11**, 58426-14-5; **12**, 58426-15-6; **13b**, 56561-19-4; **14**, 58426-16-7; **15**, 17497-52-8; **16**, 823-91-6; **17**, 35460-31-2; **18**, 58426-17-8; potassium acetone enolate, 35648-48-7; ammonium thiophenoxide, 54043-02-6; 1-(2′-norbornyl)-2-propanone, 31683-73-5; 1-indanone hydrazone, 5736-44-7; 3 iodoindene, 58426-18-9; 1-iodoindene, 58426-19-0.

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Reaction of Sulfur with 2,6-Disubstituted Phenols

Allan S. Hay* and Bernice M. Boulette

General Electric Research and Development Center, Schenectady, New York 12301

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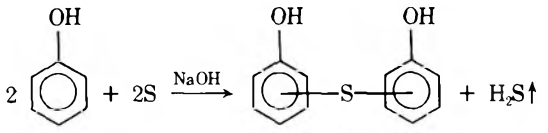
In the presence of catalytic amounts of base, no reaction occurs between 2,6-disubstituted phenols and sulfur. When epoxides or activated olefins such as acrylonitrile are continuously added to the reaction mixture, excellent yields of thiobisphenols are obtained.[1]

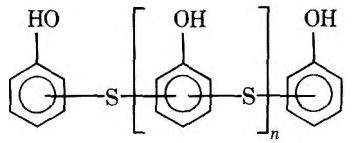
The early patent literature is replete with examples of the reactions of phenols with sulfur.[2] A typical example involves heating sulfur with phenol in the presence of a base for extended periods of time at elevated temperatures to yield resinous materials. As a side product hydrogen sulfide is evolved equivalent to approximately one-half of the sulfur introduced.

Recently Neale et al.[3] demonstrated that phenol in large excess reacts with sulfur at elevated temperatures (140–180 °C) and long times (6–24 h) according to the equation



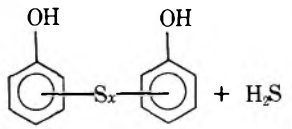
1

During the course of the reaction H_2S is slowly evolved. The three isomeric monothiobisphenols (2,2′-, 2,4′-, 4,4′-) were obtained in quantitative yield in the approximate ratio 45:45:10. When lower ratios of phenol to sulfur are used, oligomeric materials (**2**) resulting from reaction at more than one site on the phenol are obtained.



2

Geering[4] has prepared polythiobisphenols (**3**) by allowing equivalent amounts of phenol and sulfur to react at elevated



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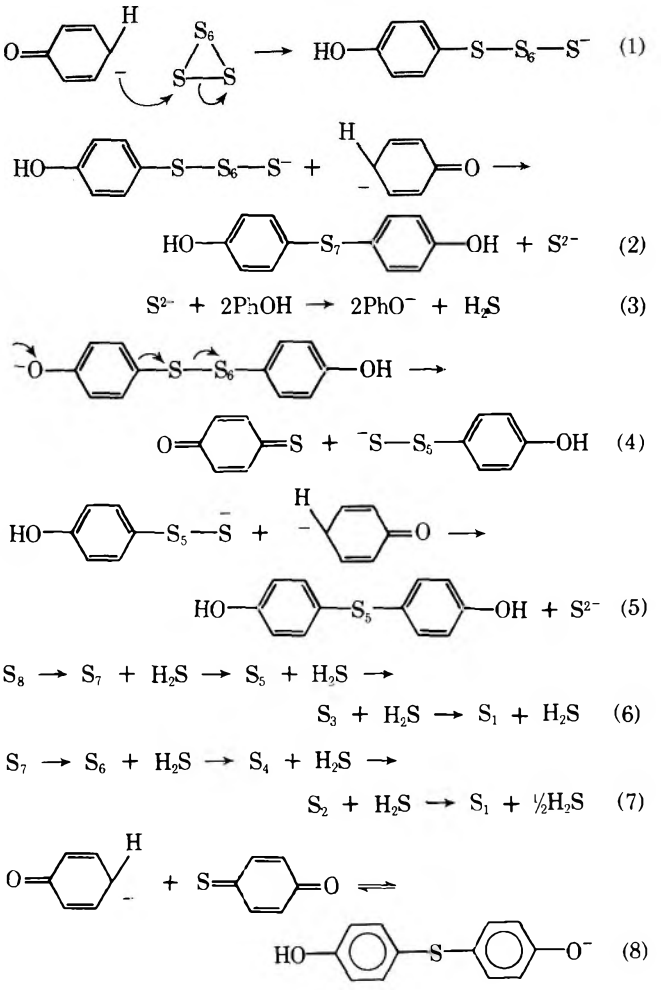
temperatures in the presence of catalytic amounts of sodium hydroxide. The reaction is carried to about 40% conversion, as measured by the H_2S evolved, and the product obtained is principally the ortho,ortho′ isomer. Subsequent hydrogenation with a cobalt sulfide catalyst yields the *o*-mercapto phenols in overall 65% yield.

Results and Discussion

When we attempted the reaction of 2,6-dimethylphenol or 2,6-diphenylphenol with sulfur and catalytic amounts of sodium hydroxide according to Neale et al., no reaction occurred. Neale et al. have proposed the mechanism outlined in Scheme I for the reaction between phenol and sulfur. The phenoxide nucleophile is regenerated by reaction 3, and this step would appear to be rate determining. When the hindered phenols, which are weaker acids, are used the equilibrium

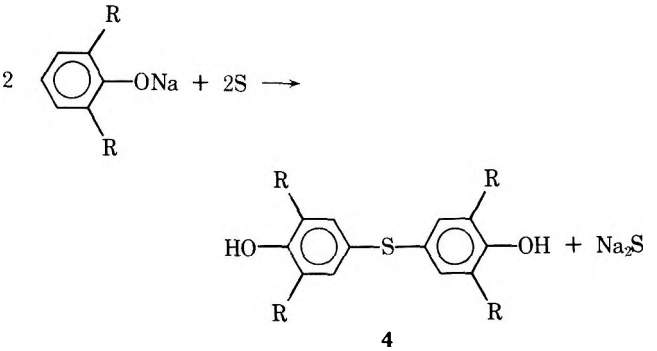
$$ArOH + HS^- \rightleftharpoons ArO^- + H_2S$$

Scheme I



would be expected to be displaced to the left, the concentration of the phenoxide ion decreased, and H_2S evolved much more slowly.

We next found that reaction of 2,6-dimethyl- or 2,6-diphenylphenol would occur to a limited extent (up to 30% conversion to the thiobisphenol 4) if stoichiometric amounts of base were used. The reaction apparently does not go to



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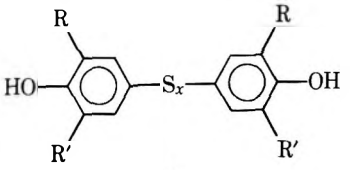
completion because of depletion of the base and sulfur as polysulfides.

Fujisawa[5] was able to treat hindered phenols with sulfur under mild conditions, refluxing ethanol in the presence of equivalent amounts of potassium hydroxide, to yield mixtures of the polythiobisphenols **5**. The higher temperatures used in



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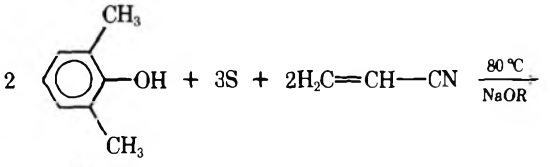
the present work are necessary to drive the reaction to the monosulfide product.

The key to improving the reaction appeared to us to be the removal of sulfide ion which can tie up sulfur as polysulfides. It appeared that what was necessary to facilitate the reaction was the addition of a species that would react with the S^{2-} or HS^- or any nucleophilic sulfur species, but not with phenoxide ion. When acrylonitrile was slowly added to a mixture of 2,6-dimethylphenol (**6**) and sulfur in the absence of a solvent and in the presence of catalytic amounts of the sodium phenoxide, 85–90% yields of thiobis(2,6-dimethylphenol) (**7**) were obtained according to the equation



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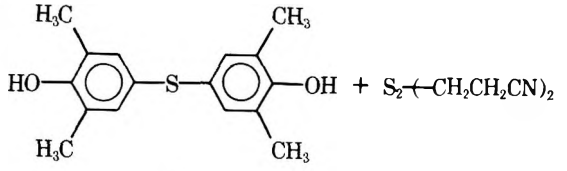

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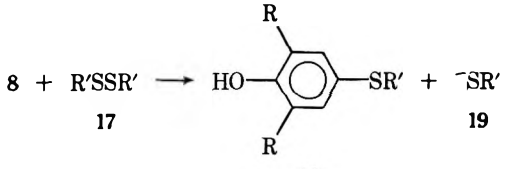
The acrylonitrile must be added slowly to the reaction mixture and the optimum temperature for the reaction is about 80 °C. At 50 °C the principal product is β-2,6-dimethylphenoxypropionitrile and at higher temperatures side reactions occur.

Continuous addition of a reagent which would react preferentially with any nucleophilic sulfur species present and at the same time regenerate phenoxide ion would be expected to alter the course of the reaction as outlined in Scheme II (R = CH_3).

Polysulfide species such as **16** would react with phenoxide ion similar to the reaction with elemental sulfur. Fujisawa[6] has demonstrated the reaction of disulfides with hindered phenoxide ions. The reaction proceeds readily when the substituents are large and bulky (*tert*-butyl, isopropyl) but they found that no reaction occurs with 2,6-dimethylphenol.



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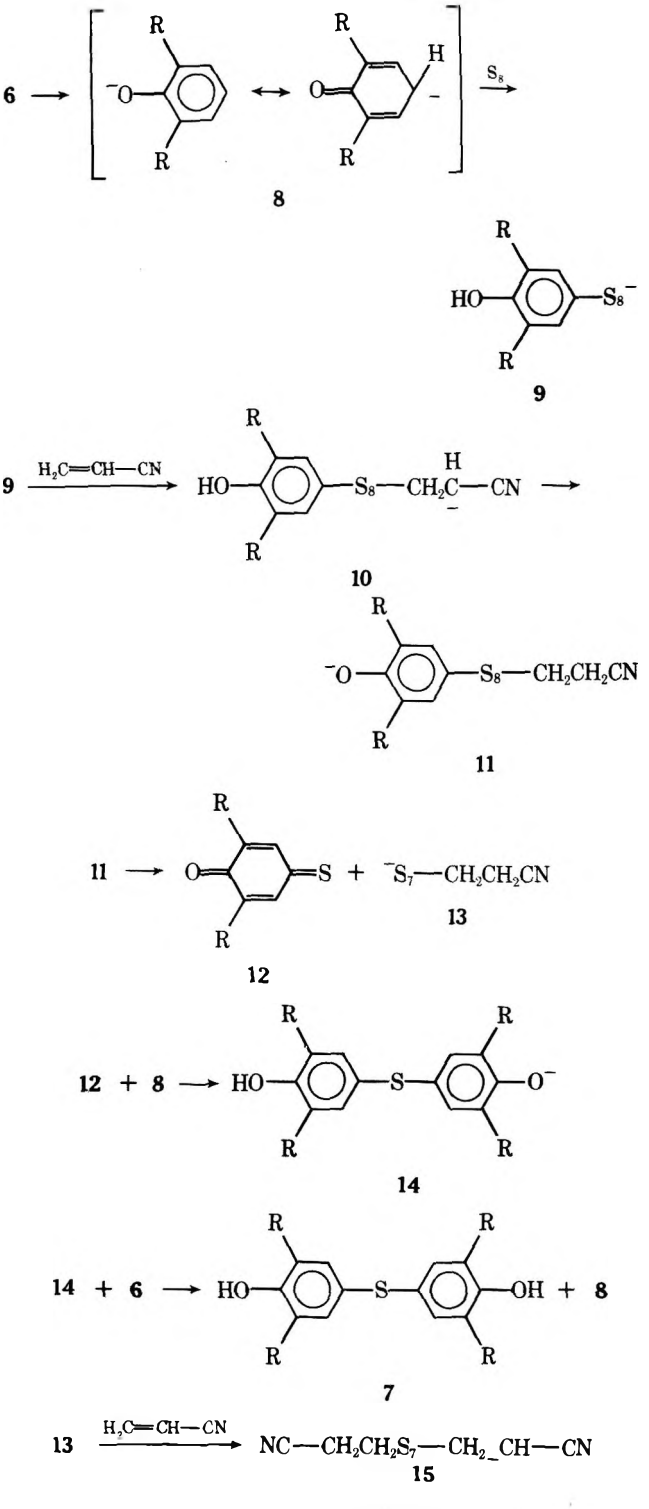
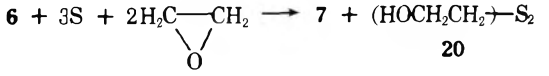
In the above postulated sequence of reactions, this would explain the preponderance of biscyanoethyl disulfide formed as a coproduct. The polysulfide species such as **16** would continue to react with phenoxide ion giving intermediates such as **11** and **13** with fewer sulfurs until the eventual products,

Scheme II



thiobisphenol and cyanoethylated disulfide, are formed. Other activated olefins such as methacrylonitrile and ethyl acrylate have been shown to function in the same manner.

The reaction with epoxides is also analogous to the reaction with the activated olefins.



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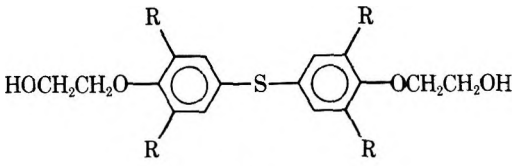
If 4 equiv of the epoxide is used, the bishydroxyethoxylated product (**21**) is obtained directly in 76% yield (isolated).



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The reaction of phenol and monosubstituted phenols with sulfur under these conditions takes a different course and will be the subject of a future publication.

Experimental Section

4,4′-Thiobis(2,6-diphenylphenol). To a 3-l., round-bottom, three-necked flask equipped with stirrer, thermometer, Dean-Stark trap, and condenser and maintained under a nitrogen atmosphere were placed 246 g (1.0 mol) of 2,6-diphenylphenol and 1230 ml of xylene. A solution of 40 g (1.0 mol) of sodium hydroxide in 80 ml of water was then added. The mixture was heated to reflux with stirring and the water removed. When removal of the water was complete, the reaction mixture was cooled to about 70–80 °C and 32 g (1.0 mol) of sulfur was added. The reaction mixture was again heated to reflux and the xylene was removed via the Dean-Stark trap until the temperature reached 169 °C. The reaction mixture was not homogeneous and vigorous stirring was needed. After 2 h, the reaction mixture was cooled and water was added. The solidified product was separated by filtration, washed well with more water and finally with pentane, and then dried in the vacuum oven overnight. The crude product was then triturated with 2 l. of hot heptane and the heptane-insoluble material was recrystallized from acetic acid. There was obtained 83.7 g (0.16 mol, 32.0% yield) of material melting at 151 °C. Recrystallization raised the melting point to 162–163 °C. Anal. Calcd for $C_{36}H_{26}O_2S$: C, 82.73; H, 5.01; S, 6.13. Found: C, 82.4; H, 4.98; S, 5.9.

General Procedure for the Reaction of 2,6-Dimethylphenol and Sulfur in the Presence of Acrylonitrile or Alkylene Oxides. A. Acrylonitrile. To a 500-ml round-bottom flask equipped with a Vibromixer stirrer , condenser, and thermometer with temperature controller attached, there was added 122.2 g (1.0 mol) of 2,6-xylenol and 2.3 g (0.1 g-atom) of sodium metal. The reaction mixture was heated under N_2 until the sodium dissolved, then cooled. There was added 48.0 g (1.5 g-atoms) of sulfur and the reaction mixture was heated and maintained at 80 °C. Over a period of 4.25 h there was added 53.0 g. (1.0 mol) of acrylonitrile. During this period the sulfur slowly went into solution. The reaction mixture was cooled and after diluting with ether it was washed with 10% hydrochloric acid and then with water until neutral. The ether was then removed by distillation to yield 201.6 g of crude product. The unreacted 2,6-xylenol (24.0 g) was removed by distillation at 0.2 mm, leaving a residue of 177.6 g. The residue was dissolved in ether and washed with 10% sodium hydroxide solution, leaving 12.1 g of base-insoluble material, principally β,β′-dithiodipropionitrile. After acidification with dilute hydrochloric acid the base-soluble fraction weighed 139.7 g. Recrystallization from heptane yielded 90.7 g (66.2% yield) of thiobis(2,6-dimethylphenol), mp 124 °C.

B. Propylene Oxide. 1. 2 Equiv. The reaction was performed in the same manner as the preceding example using 122.2 g (1.0 mol) of 2,6-xylenol, 1.2 g (0.05 g-atom) of sodium, 4.8 g (1.5 g-atoms) of sulfur, and 58.1 g (1.0 mol) of propylene oxide. The reaction was performed at 100 °C and the propylene oxide was added over a 4-h period. There was obtained 17.7 g (0.15 mol) of unreacted 2,6-xylenol (conversion 85%), 20.9 g (0.12 mol) of 2,6-dimethylphenoxy-2-propanol, 100.0 g (0.73 mol, 85.8% yield) of thiobisxylenol, and 3.4 g of the mono-O-alkylated thiobisxylenol.

When this reaction was performed at 50 °C, the only significant product was 2,6-dimethylphenoxy-2-propanol.

2. 4 Equiv. The reaction was performed as above except that an additional 2 mol of propylene oxide was added in the same time period. After the addition was complete, there was added 50 ml of 20% sodium hydroxide solution and the reaction was maintained at temperature for 30 min. The reaction mixture was then cooled, washed with water, and distilled. There was obtained a 76% yield of 4,4′-thiobis[1-(2,6-dimethylphenoxy)-2-propanol], mp 90–92 °C. Anal. Calcd for $C_{22}H_{30}O_4S$: C, 67.67; H, 7.74; S, 8.20. Found: C, 67.40; H, 7.98; S, 8.3.

C. Ethylene Oxide. Reactions with ethylene oxide were performed as above except that introduction of the ethylene oxide from a cylinder was continued until completion of the reaction was indicated by gas chromatography.

4,4′-Thiobis[2-(2,6-dimethylphenoxy)ethanol]. Yield 67%; mp 99 °C. Anal. Calcd for $C_{20}H_{26}O_4S$: C, 66.28; H, 7.23; S, 8.83. Found: C, 66.4; H, 7.2; S, 8.9.

Registry No.—4 (R = Ph), 58426-07-6; **6**, 576-26-1; **7**, 18525-99-0; **21** (R = CH_3), 58426-08-7; sulfur, 7704-34-9; acrylonitrile, 107-13-1; propylene oxide, 75-56-9; 4,4′-thiobis[1-(2,6-dimethylphenoxy)]-2-propanol, 58426-09-8; 2,6-diphenylphenol, 2432-11-3; ethylene oxide, 75-21-8.

References and Notes

(1) Presented in part at the VIth Symposium on Organic Sulphur Chemistry, Bangor, U.K., July 1974.
(2) For leading references, see C. Ellis, "The Chemistry of Synthetic Resins", Reinhold, New York, N.Y., 1935.
(3) A. J. Neale, P. J. S. Bain, and T. J. Rawlings, *Tetrahedron*, **25**, 4583, 4593 (1969).
(4) E. J. Geering, U.S. Patent 3 717 682 (Feb 20, 1973).
(5) T. Fujisawa, K. Hata, and T. Kojima, *Synthesis*, **5**, 38 (1973).
(6) T. Fujisawa and T. Kojima, *J. Org. Chem.*, **38**, 687 (1973).

Stereochemistry of Nucleophilic Addition Reactions. Addition of Thiophenol to Ethyl 4-*tert*-Butylcyclohexene-1-carboxylate

Rudolph A. Abramovitch* and Sandra S. Singer

Department of Chemistry, University of Alabama, University, Alabama 35486

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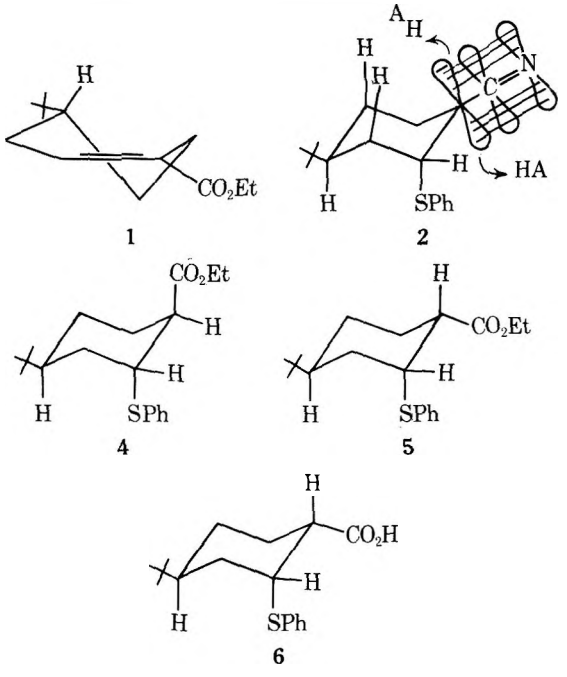
The addition of thiophenoxide ion to ethyl 4-*tert*-butylcyclohexene-1-carboxylate gives the two products **4** and **5** containing an axial thiophenoxy group. The stereochemistries of the products were established by a combination of NMR spectroscopy and chemical transformations into compounds of known stereochemistry. Under conditions of kinetic control the ratio of **4** to **5** was 5.5:94.5. Under conditions of thermodynamic control it was 14:86. The results are discussed. A number of sulfones in this series were also prepared and their NMR spectra discussed.

In previous papers in this series we have described the nucleophilic addition of malonate anion to two activated olefins of biased conformation, namely 4-*tert*-butyl-1-cyanocyclohexene[1] and ethyl 4-*tert*-butylcyclohexene-1-carboxylate (1),[2] and the addition of thiophenoxide ion and of hydrogen chloride to the above unsaturated nitrile.[3] In the additions of the malonate anion, the main product formed in protic solvents under conditions of kinetic control is the equatorial malonate, with an axial nitrile or ethoxycarbonyl compound. Under conditions of thermodynamic control the diequatorial product predominates. In the addition of thiophenoxide to the unsaturated nitrile, kinetic and thermodynamic control of the addition gave the axial thiophenoxy, equatorial nitrile isomer as the main product, but the pro-

portion of diaxial isomer was much greater under thermodynamic than under kinetic control conditions. These results were explained as follows: the preferred equatorial approach of the bulky malonate was attributed[1] to large diaxial nonbonded interactions in the transition state for axial addition, which transition state was assumed to resemble the intermediate. With smaller nucleophiles such as PhS^- and Cl^- such 1,3-diaxial repulsions would be less important, and axial approach of the nucleophile would be favored because of almost continuous overlap between the developing σ bond and the conjugated system in the formation of the transition state leading to axial product.[3] Kinetically controlled protonation of the intermediate anion from the least hindered side would account nicely for the observed stereoselectivities. Thus, in the case of the intermediate anion (**2**) from the axial addition of thiophenoxide to 4-*tert*-butyl-1-cyanocyclohexene protonation would involve approach from the side remote from the hindering thiophenoxy group.



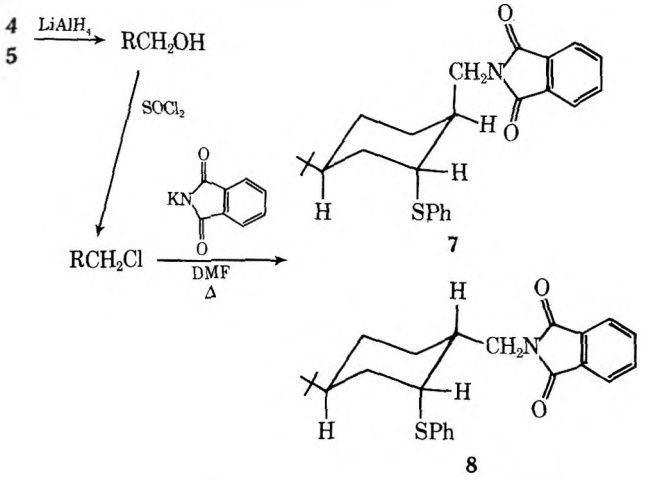
It was of interest to determine the preferred stereochemistry of kinetically controlled addition and protonation in the case where the linear nitrile group in **2** would be replaced by the bulkier carbethoxy group which could give rise to $A^{(1,3)}$ strain with an equatorial 2 substituent,[4] but in which relief of such a strain by chair–chair interconversion is not possible owing to the presence of the 4-*tert*-butyl group. To this end the addition of thiophenoxide ion to **1** under various conditions was studied.

In contrast to the addition of thiophenoxide ion (**3**) to 4-*tert*-butyl-1-cyanocyclohexene, which, under suitable conditions, gave three isomeric adducts, the addition of **3** to **1** gave only two adducts under all the experimental conditions examined. These proved to he *r*-1-*tert*-butyl-*c*-4-carbethoxy-*t*-3-thiophenoxycyclohexane (**4**) and *r*-1-*tert*-butyl-*t*-4-carbethoxy-*t*-3-thiophenoxycyclohexane (**5**). Under kinetic control conditions[3] (ethanolic sodium ethoxide, 25 °C, 42 days) **5** was the main product, **4**:**5** = 5.5:94.5. Under thermodynamic control conditions (NaOEt–EtOH, 80 °C)[3] **4**:**5** = 14:86, corresponding to $\Delta G°_{COOEt} = -1.2$ kcal/mol, in excellent agreement with the literature value of −1.1 to −1.2 kcal/mol.[5]

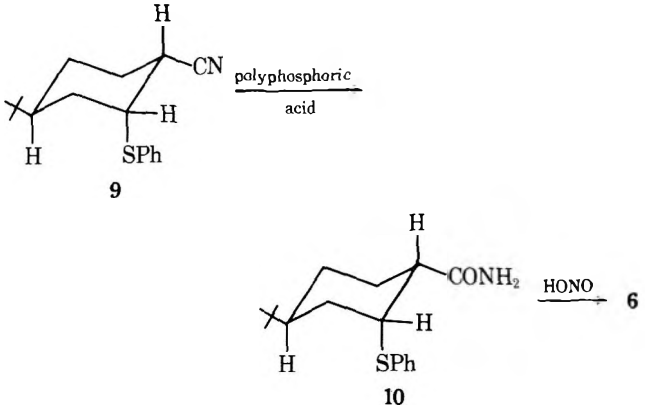
The assignment of the configurations to **4** and **5** was based initially mainly on the proton magnetic resonance spectra of the isomers. While the proton geminal to the ethoxycarbonyl group was clearly visible, that α to the thiophenoxyl group was obscured by the ethoxycarbonyl methylene group. In **4** the C-4 proton appears as an unresolved broad singlet at δ 2.67, thus suggesting an axial $-CO_2Et$ group. In **5** this proton gives rise to a doublet of doublet of doublets at δ 2.50 ($J_{4a,5a} = 11$, $J_{3e,4a} = J_{4a,5e} = 5$ Hz), indicating an equatorial CO_2Et group and possibly an axial PhS residue (giving rise to the low $J_{3e,4a}$ value). Since **4** and **5** are in equilibrium with each other,[6] this suggests that the thiophenoxy group is axial in **4** as well.

Hydrolysis of **5** with 3 N HCl gave the acid **6** whose configuration could be established unambiguously by ^1H NMR. The C-4 proton gave rise to a broad multiplet at δ 2.60 ($J_{4a,5a} = 12$, $J_{3e,4a} = J_{4a,5e} = 3.5$ Hz, axial H), while the C-3 proton gave rise to a broad doublet at δ 3.90 ($J_{3e,4a} = 3.5$ Hz, equatorial H).

The assigned stereochemistries could be confirmed chemically by the conversion of each of the stereoisomers **4** and **5** to the known[3] phthalimides **7** and **8**, respectively, via the corresponding alcohols and chlorides:



Alternatively, **5** could be correlated with *r*-1-*tert*-butyl-*t*-3-thiophenoxy-*t*-4-cyanocyclohexane (**9**) by conversion of the latter to **6** via the amide **10**.



Some important ^1H NMR data for the compounds described above are summarized in Table I. As has already been pointed out,[3] all equatorial side-chain methylene groups in this series give rise to an eight-line AB multiplet of an ABX system owing to the nonequivalence induced by the anisotropy of the vicinal axial thiophenoxy group. Axial methylenes give rise to broad doublets (A_2X).

The addition of thiophenoxide to **1** is thus analogous to the addition to the corresponding cyano olefin in that axial addition of thiophenoxide is followed by protonation from the least hindered side, i.e., that remote from the axial thiophenoxyl group, to give the product of trans-diaxial addition **5** as the kinetically controlled product. Since this is also the thermodynamically more stable isomer it is also the main product of addition under conditions of thermodynamic

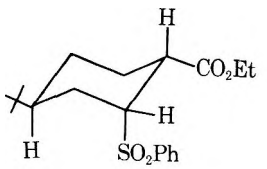
Table I. Selected ^{1}H NMR Chemical Shifts for *r*-1-*tert*-Butyl-*t*-3-thiophenoxyl-4-X-cyclohexanes

Registry no.	X (*c* or *t*)	C-4 H δ	CH_2Y δ	C-3 H δ
58463-31-3	*c*-4-CO_2Et	2.67 s		
58463-32-4	*t*-4-CO_2Et	2.50 d of t		
58463-33-5	*t*-4-CO_2H	2.60 d of t		3.90
58463-34-6	*t*-4-CH_2OH		3.60 ABX	3.72 s
58463-35-7	*c*-4-CH_2OH		3.50 br d	3.66 s
58463-36-8	*t*-4-CH_2Cl		3.60 ABX	3.70 s
58463-37-9	*c*-4-CH_2Cl		3.52 br d	3.70 s
35905-89-6	*t*-4-CH_2NR_2[a]		3.60 ABX	3.60 s
35905-93-2	*c*-4-CH_2NR_2[a]		3.68 br d	3.38 s

[a] R = phthalimido.

control. A$^{(1,3)}$ strain between the bulkier (than nitrile) ethoxycarbonyl group and an equatorial substituent does not come into play since only axial addition is observed. The results thus support the generalization proposed to rationalize the protonation of 2-substituted cyclohexyl anions.[6] The only difference between the additions reported here and those to the unsaturated nitrile is that, in the latter case, some equatorial thiophenoxy derivative was formed in THF and in DMF. This was not the case in the additions of thiophenoxide to **1**. That this is not due solely to the greater A$^{(1,3)}$ interactions possible in the transition state by the CO_2Et group than by the linear nitrile is clear since in the case of the addition of the bulkier diethyl malonate anion equatorial addition does occur.

Some very interesting and unusual relative stabilities of *tert*-butyl-3-phenylsulfonyl-4-phthalimidomethylcyclohexanes were reported and discussed earlier.[3] It was of interest, therefore, to prepare the sulfones corresponding to the phenylthio derivatives described above. Oxidation of **5** with peracetic acid gave the sulfone ester **11**. Similar oxidation of **4** led to a mixture of epimers, **12** and **13** on one occasion, but this result was not reproducible: in other similar oxidations, no **13** was formed. No explanation of this discrepancy is available. Authentic **13** was synthesized from *r*-1-*tert*-butyl-*c*-4-cyano-*c*-3-thiophenoxycyclohexane[3] by oxidation to the sulfone, hydrolysis to the amide with polyphosphoric acid, treatment with nitrous acid to give the sulfone acid, and then esterification. The ^{1}H NMR of **11** was interesting. The C-4 proton gave rise to a doublet of triplets at δ 2.70 (J_{aa} = 11, J_{ae} = 4.5 Hz) while the C-3 proton signal could be discerned at δ 3.84, buried under the methylene absorption. The ester



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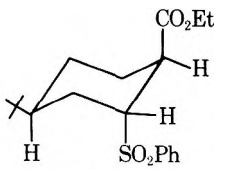

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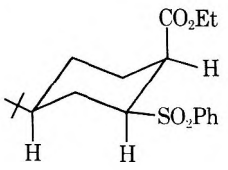

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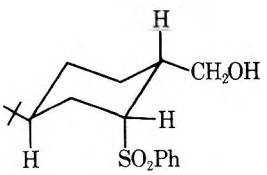

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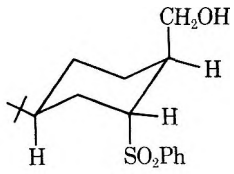

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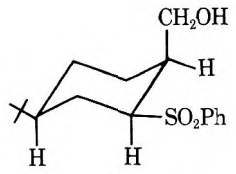

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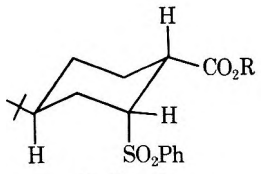


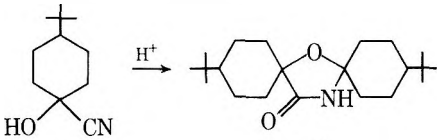
17, R = H

18, R = Me

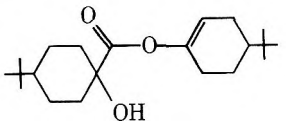
methylene gave rise to a complex 16-line multiplet, as is predicted for an ABX_3 system.[8] This suggests that free rotation of the ethoxyl group is greatly restricted, either sterically or by electronic repulsions between the $PhSO_2$ and ester oxygens, so that the methylene protons constitute an AB system. Other recent examples of magnetic nonequivalence of ethyl ester methylene protons have been reported.[1,9,10] In the ester sulfone **12** this situation cannot obtain and the ester methylene protons gave rise to a quartet at δ 4.08. As expected, the ester methylene group in **13** gave rise to a complex multiplet which simplified to an AB multiplet on irradiation of the ester methyl group.

Other sulfones synthesized at this time are the alcohols **14**, **15**, and **16**, the acid **17**, and the ester **18** (see Experimental Section). No unusual features appeared in their NMR spectra except that the carboxyl proton in **17** resonated at δ 9.26, which is higher than the normal range reported (δ 11.5–12.5)[11] for such protons. This could be due to shielding of the carboxyl proton by the π cloud of the phenyl group.

During preliminary studies on the synthesis of **1**, ethanolysis of cyanohydrin **19** was studied. This gave rise to a troublesome by-product with little of the desired hydroxy ester formed. The by-product's spectral and analytical data corresponded to those expected for dispiro[bis(4-*tert*-butylcyclohexane-1,2′,5′,1″-oxazolid-4′-one)] (**20**), $C_{21}H_{37}NO_2$. This compound is identical with the one prepared earlier[12] and also with the one prepared by treatment of **19** with polyphosphoric acid,[13] to which had been attributed[12] structure **21**. The calculated values for the C and H analyses of **20** and **21** are very similar.



19 **20**



21

Experimental Section

Addition of Thiophenol to Ethyl 4-*tert*-Butylcyclohexane-1-carboxylate. A. Kinetic Control Conditions. Sodium (4.38 g, 0.19 mol) was dissolved in absolute ethanol (200 ml). Thiophenol (31.4 g, 0.286 mol) and ethyl 4-*tert*-butylcyclohexane-1-carboxylate (20 g, 0.095 mol) were added. The flask was flushed with dry, oxygen-free nitrogen, and allowed to stand at room temperature for 42 days. The solution was acidified with glacial acetic acid, basified with 5% aqueous NaOH, and extracted with ether (4 × 200 ml). The combined extracts were washed with 5% NaOH (2 × 200 ml) and brine (2 × 200 ml), dried ($MgSO_4$), and evaporated. Unreacted olefin was removed by vacuum distillation. The residue (8.5 g) was dissolved in light petroleum (bp 30–60 °C). GLC analysis (20% SE-30 on 60–100 mesh Chromosorb

W, 6 ft × 3/16 in., 245 °C, 60 ml/min flow rate of helium carrier gas) indicated the presence of two compounds which were subsequently shown to be the isomeric ester sulfides **4** and **5** in the molar ratio of 5.5:94.5. The major product, ethyl *r*-1-*tert*-butyl-*t*-3-thiophenoxycyclohexane-*t*-4-carboxylate (**5**), crystallized from light petroleum: mp 58–59 °C (from light petroleum); ir (KBr) 3060 (aromatic C–H), 1720 cm^{-1} (ester C=O); NMR (CCl_4) δ 7.35 (m, 5, ArH), 3.88 (m, 3, $COOCH_2CH_3$ and C_3 H), 2.50 (d of t, J_{aa} = 11, J_{ae} = 5 Hz, 1, C_4 H), 0.87 (s, 9, *tert*-butyl); mass spectrum (70 eV) *m/e* (rel intensity) 320 (16) ($M^{\cdot+}$), 155 (17), 154 (20), 137 (55), 121 (15), 110 (42), 109 (34), 108 (16), 57 (100).

Anal. Calcd for $C_{19}H_{28}O_2S$: C, 71.20; H, 8.81. Found: C, 71.28; H, 8.46.

The minor product was resolved by column chromatography of the mother liquor (vide supra) on silica gel (benzene–light petroleum, 4:6 v/v, as eluent) to give ethyl *r*-1-*tert*-butyl-*t*-3-thiophenoxycyclohexane-*c*-4-carboxylate (**4**): bp 144–148 °C (0.25 mm); ir (neat) 3060, 3050 (aromatic C–H), 1725 cm^{-1} (ester C=O); NMR (CCl_4) δ 7.10 (m, 5, ArH), 4.04 (m, 3, $COOCH_2CH_3$ and C_3 H), 2.67 (br s, 1, C_4 H), 1.18 (t, 3, $COOCH_2CH_3$), 0.87 (s, 9, *tert*-butyl); mass spectrum (70 eV) *m/e* (rel intensity) 320 (11) ($M^{\cdot+}$), 154 (15), 137 (33), 110 (32), 109 (27), 57 (100).

Anal. Calcd for $C_{19}H_{28}O_2S$: C, 71.20; H, 8.81. Found: C, 70.77; H, 8.76.

Thermodynamic Control Conditions. Sodium (19.8 g, 0.86 mol) was dissolved in absolute ethanol (860 ml). Thiophenol (150 g, 1.29 mol) and ethyl 4-*tert*-butylcyclohexane-1-carboxylate (90 g, 0.43 mol) were added. The solution was boiled under reflux for 75 h. It was then worked up as described in the previous experiment. The product mixture (121 g, 90%) was dissolved in light petroleum. GLC of the mixture (conditions as given in the preceding experiment) indicated the presence of the two isomeric ester sulfides **4** and **5** in the molar ratio of 14:86. A white solid crystallized (56 g) from the solution of the product mixture. It was identified as **5**, its melting point, ir, and NMR spectra being identical with those of the material previously obtained. The mother liquor was chromatographed on silica gel to obtain the other isomer (4 g), which was shown to be the *r*-1, *t*-3, *c*-4 ester sulfide (**4**), identical with material previously obtained.

Addition in Dimethylformamide. Lithium thiophenolate (0.53 g, 5 mmol), ethyl 4-*tert*-butylcyclohexene-1-carboxylate (1.05 g, 5 mmol), and thiophenol (1.6 g, 15 mmol) were dissolved in dimethylformamide (10 ml). The solution was boiled under reflux for 6 h, cooled, poured into water (40 ml), and extracted with ether (3 × 20 ml). The combined ether extracts were washed with 5% NaOH (3 × 20 ml) and brine (2 × 20 ml), dried ($MgSO_4$), and evaporated. GLC analysis of the residual oil (conditions given previously) indicated the presence of unreacted olefin and the two isomeric ester sulfides (**4** and **5**) in the ratio of 1.2:1. The two products were separated by column chromatography (total yield 100 mg, 6.3%) and were identical in every respect with the compounds obtained with ethanol as solvent.

Equilibration of the *r*-1, *t*-3, *t*-4 Ester Sulfide (5). *r*-1-*tert*-Butyl-*t*-4-carbethoxy-*t*-3-thiophenoxycyclohexane (**5**, 640 mg, 2 mmol) was added to a solution of sodium (92 mg, 4 mmol) and thiophenol (0.66 ml, 6 mmol) in absolute ethanol (4 ml). The solution was boiled under reflux for 5 days, and worked up as described previously. GLC analysis of the residual oil (0.513 g) indicated the presence of the isomeric ester sulfides **4**:**5**, 9:91. The isomers were separated by column chromatography on silica gel (50 g) using benzene–light petroleum (1:1 v/v) as eluent and had infrared spectra identical with those of material obtained previously.

Attempted Equilibration of the *r*-1, *t*-3, *c*-4 Ester Sulfide (4). *r*-1-*tert*-Butyl-*c*-4-carbethoxy-*t*-3-thiophenoxycyclohexane (**4**, 0.320 g, 1 mmol) was dissolved in a solution of sodium (46 mg, 2 mmol) and thiophenol (0.33 ml, 3 mmol) in absolute ethanol (2 ml). The solution was boiled under reflux for 5 days. It was then worked up as described previously. GLC analysis of the residual oil (0.224 g) indicated that very little equilibration had occurred. The oil was dissolved in a solution of sodium ethoxide and thiophenol and the solution was boiled under reflux for 2 weeks. The reaction was worked up as described previously. GLC analysis of the residual oil (0.118 g) indicated the presence of the isomeric ester sulfides **4**:**5**, 55:45. The isomers were separated by column chromatography and had ir spectra identical with those of material obtained previously.

The equilibration was repeated in a sealed tube heated at 120° for 1 week. GLC analysis of the oil obtained on workup indicated the presence of the isomeric ester sulfides in the ratio **4**:**5**, 67:33.

***r*-1-*tert*-Butyl-*t*-4-hydroxymethyl-*t*-3-thiophenoxycyclohexane.** The *r*-1, *t*-3, *t*-4 ester sulfide (**5**, 3.2 g, 10 mmol) in dry ether (10 ml) was added dropwise to a solution of lithium aluminum hydride (0.53 g, 15 mmol) in dry ether (6 ml) at such a rate as to maintain gentle reflux. The solution was stirred at room temperature for 1 h after the addition was completed. The excess lithium aluminum hydride was decomposed with ethanol, the mixture poured into 1 N HCl (100 ml), the ether layer removed, and the aqueous layer extracted with ether (4 × 25 ml). The combined ether extracts were dried ($MgSO_4$) and evaporated to give an oil (2.58 g, 96%). This solidified on standing and was recrystallized from *n*-hexane to give white crystals of the alcohol: mp 58.5–60 °C; ir (KBr) 3350 cm^{-1} (OH); NMR (CCl_4) δ 7.26 (m, 5, ArH), 3.72 (br s, 1, C_3 H), 3.60 (m, 2, **ABX**, CH_2OH), 2.63 (s, 1, OH, exchangeable with D_2O), 0.88 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{17}H_{26}OS$: C, 73.34; H, 9.41. Found: C, 73.60; H, 9.36.

***r*-1-*tert*-Butyl-*c*-4-hydroxymethyl-*t*-3-thiophenoxycyclohexane.** The diaxial alcohol was prepared from the corresponding ester in the same manner as was the alcohol from **5** (0.53 g, 66%): bp 120–124 °C (0.007 mm); ir (neat) 3350 cm^{-1} (OH); NMR (CCl_4) δ 7.20 (m, 5, ArH), 3.66 (br s, 1, C_3 H), 3.50 (br d, 2, CH_2OH), 3.30 (s, 1, OH, exchangeable with D_2O), 0.90 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{17}H_{26}OS$: C, 73.34; H, 9.41. Found: C, 73.67; H, 9.44.

***r*-1-*tert*-Butyl-*t*-4-chloromethyl-*t*-3-thiophenoxycyclohexane.** The *r*-1, *t*-3, *t*-4 alcohol (1.65 g, 6 mmol) and thionyl chloride (2.14 g, 18 mmol) were boiled under reflux for 6.5 h. Excess thionyl chloride was removed in vacuo and the residue was dissolved in ether (30 ml). The ethereal solution was washed with water (2 × 30 ml), 5% aqueous NaOH (2 × 30 ml), and brine (2 × 30 ml), dried ($MgSO_4$), and evaporated. The yellow residual oil (1.3 g, 73%) had bp 140–144 °C (0.025 mm); ir (neat) no OH; NMR (CCl_4) δ 7.30 (m, 5, ArH), 3.70 (s, 1, C_3 H), 3.60 (m, 2, **ABX**, CH_2Cl), 0.90 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{17}H_{25}ClS$: C, 68.74; H, 8.49. Found: C, 68.42; H, 8.45.

***r*-1-*tert*-Butyl-*c*-4-chloromethyl-*t*-3-thiophenoxycyclophexane.** This was prepared from the corresponding alcohol as described for the *r*-1, *t*-3, *t*-4 isomer. The chloride (0.212 g, 73%) had bp 106–110 °C (0.005 mm); ir (neat) no OH; NMR (CCl_4) δ 7.20 (m, 5, ArH), 3.70 (br s, 1, C_3 H), 3.52 (br d, 2, CH_2Cl), 0.90 (s, 9, *tert*-butyl); mass spectrum *m/e* 298, 296 ($M^{\cdot+}$). The crude material was used directly in the conversion to the corresponding phthalimide.

***r*-1-*tert*-Butyl-*c*-4-phthalimidomethyl-*t*-3-thiophenoxycyclohexane.** The above *r*-1, *t*-3, *c*-4 chloride (0.20 g, 0.172 mmol) and potassium phthalimide (0.463 g, 2.5 mmol) were dissolved in dimethylformamide (2 ml). The reaction was carried out as described below for the *r*-1, *t*-3, *t*-4-isomer. The *r*-1, *t*-3, *c*-4 phthalimide (**7**, 81 mg, 29%) was recrystallized from ethanol–water and had mp 85–89 °C (lit.[3] 90–92.5 °C), identical in all respects with the compound previously obtained.

***r*-1-*tert*-Butyl-*t*-4-phthalimidomethyl-*t*-3-thiophenoxycyclohexane (8).** The *r*-1, *t*-3, *t*-4 chloride (0.297 g, 1 mmol) and potassium phthalimide (0.740 g, 4 mmol) were dissolved in dimethylformamide (4 ml). The solution was boiled under reflux for 24 h, diluted with water (5 ml), and extracted with ether (3 × 15 ml). The desired phthalimide was separated from starting material by column chromatography on silica gel (starting with light petroleum as eluent and gradually adding benzene). The phthalimide (177 mg, 44%) was eluted with benzene–light petroleum (4:1 v/v) and was recrystallized from ethanol–water to give white crystals: mp 144–146 °C (lit.[3] 144–145 °C); ir (KBr) 1770, 1710 cm^{-1} (C=O); NMR (CCl_4) δ 7.50 (m, 9, ArH), 3.60 (m, 3, **ABX**, CH_2NR_2 and C_3 H), 0.94 (s, 9, *tert*-butyl), identical with an authentic sample.

***r*-1-*tert*-Butyl-*t*-3-thiophenoxycyclohexane-*t*-4-carboxylic Acid (6).** The *r*-1, *t*-3, *t*-4 ester (**5**, 2.72 g, 8.5 mmol) and 3 N HCl were boiled under reflux for 132 h. The mixture was cooled, diluted with water (50 ml), and extracted with ether. The combined ether extracts were washed with 5% NaOH (4 × 30 ml). Three layers were formed, a small brown layer being present between the ethereal and aqueous layer. The middle layer was the sodium salt of the desired acid and was taken with the aqueous layer. The aqueous mixture was acidified to pH 1, and the white precipitate was filtered to give the *r*-1, *t*-3, *t*-4 acid (**6**, 0.60 g, 24%): mp 164.5–166 °C (acetone–water); ir (KBr) 3200–2500, 1705 cm^{-1} (C=O); NMR (CCl_4) δ 7.25 (m, 5, ArH), 3.90 (d, J_{ae} = 3.5 Hz, 1, C_3 H), 2.60 (d of t, J_{ae} = 12, J_{ae} = 3.5 Hz, 1 H, C_4 H), 0.82 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{17}H_{24}O_2S$: C, 69.82; H, 8.27. Found: C, 69.50; H, 8.33.

The same acid could be obtained (88%) by diazotization of the *r*-1, *t*-3, *t*-4 sulfide amide.[3]

***r*-1-*tert*-Butyl-*t*-3-thiophenoxycyclohexyl-*t*-4-carboxamide (10).** The *r*-1, *t*-3, *t*-4 nitrile sulfide (**9**, 2 g, 7 mmol) and polyphosphoric acid (20 g) were warmed on a steam bath for 5 h. The mixture

was poured into water (100 ml) and extracted with ether (2 × 100 ml). The extracts were evaporated and the residue resolved by column chromatography on silica gel (50 g). Elution with ether gave the *r*-1, *t*-3, *t*-4 amide sulfide (**10**, 1.7 g, 80%): mp 160.5–161.5 °C (aqueous ethanol); ir (KBr) 3390, 3220, 1645, 1615 cm^{-1}; NMR ($CDCl_3$) δ 7.30 (m, 5 H, ArH), 5.98 (br s, 2 H, $CONH_2$), 3.87 (d, J_{ae} = 5 Hz, 1 H, C_3 H), 2.55 (d to t, J_{aa} = 12, J_{ae} = 5 Hz, 1 H, C_4 H), 0.81 (s, 9 H, *tert*-butyl).

Anal. Calcd for $C_{17}H_{25}NOS$: C, 70.07; H, 8.65. Found: C, 69.73; H, 8.76.

***r*-1-*tert*-Butyl-*t*-3-thiophenoxycyclohexyl-*c*-4-carboxamide.** The *r*-1, *t*-3, *c*-4 nitrile (1.53 g, 0.57 mol) was heated at 80 °C with polyphosphoric acid (20 g) for 9 h. The mixture was poured into water (100 ml) and extracted with $CHCl_3$ (4 × 100 ml). The extracts were washed with 5% NaOH (200 ml) and brine (3 × 200 ml), dried ($MgSO_4$), and evaporated to give a yellow oil (1.19 g, 68%) which solidified. Recrystallization from aqueous ethanol gave the amide: mp 117.5–118.5 °C; ir (KBr) 3310, 3180, 1660, 1605 cm^{-1}; NMR ($CDCl_3$) δ 7.35 (m, 5 H, ArH), 4.08 (br s, 1 H, C_3 H), 2.58 (br s, 1 H, C_4 H), 0.78 (s, 9 H, *tert*-butyl).

Anal. Calcd for $C_{17}H_{25}NOS$: C, 70.07; H, 8.65. Found: C, 69.99; H, 8.79.

***r*-1-*tert*-Butyl-*t*-3-thiophenoxycyclohexane-*t*-4-carboxylic Acid (6) from the Amide.** The amide **10** (0.11 g, 0.38 mmol) in glacial acetic acid (3 ml) containing sulfuric acid (2.12 ml) and water (1.64 ml) at 0 °C was treated with sodium nitrite (0.10 g) slowly. After being stirred at 0 °C for 1 h the mixture was kept at room temperature overnight. It was diluted with water (20 ml) and extracted with ether and the ether evaporated. The residue (0.097 g, 88%) was identical (ir) with an authentic sample of the acid.

A similar reaction using the *r*-1, *t*-3, *c*-4 amide was unsuccessful, starting material being recovered. Repeated diazotizations led to a mixture of at least five products which were not examined further.

Ethyl *r*-1-*tert*-Butyl-*t*-3-phenylsulfonylcyclohexane-*t*-4-carboxylate (11). The *r*-1, *t*-3, *t*-4 ester sulfide (**5**, 1.5 g) was dissolved in a mixture of glacial acetic acid (25 ml), 30% hydrogen peroxide (1.5 ml), and concentrated sulfuric acid (2 drops). The solution was stirred at room temperature for 9 h, the solvent was evaporated, and the residue (1.28 g, 78%) was recrystallized from aqueous ethanol to give the sulfone **11**: mp 148–148.5 °C; ir (KBr) 1715 (C=O), 1330, 1140 cm^{-1} (SO_2); NMR ($CDCl_3$) δ 7.80, 7.50 (m, 5 H, ArH), 4.00 (m, **ABX**$_3$, 2 H, $CO_2CH_2CH_3$), 3.84 (br s, 1 H, C_3 H), 2.70 (d of t, J_{aa} = 11, J_{ae} = 4.5 Hz, 1 H, C_4 H), 1.28 (t, 3 H, $CO_2CH_2CH_3$), 0.90 (s, 9 H, *tert*-butyl).

Anal. Calcd for $C_{19}H_{28}O_4S$: C, 64.74; H, 8.01. Found: C, 64.61; H, 8.13.

Oxidation of the *r*-1, *t*-3, *c*-4 Ester Sulfide (4). The sulfide (0.15 g) was dissolved in peracetic acid solution (7 ml) [from glacial acetic acid (50 ml), 30% hydrogen peroxide (3.0 ml), and concentrated sulfuric acid (4 drops)] and stirred at room temperature for 7.75 h. The solvent was evaporated and the residue was resolved by column chromatography on silica gel (40 g). Elution with chloroform–benzene (1:1 v/v) gave the *r*-1, *t*-3, *c*-4 ester sulfone (**12**, 93 mg, 55%): bp 160 °C (0.007 mm) (with some decomposition); ir (film) 1725 (C=O), 1310, 1150 cm^{-1} (SO_2); NMR ($CDCl_3$) δ 7.85, 7.55 (m, 5 H, ArH), 4.08 (q, *J* = 7 Hz, 2 H, $CO_2CH_2CH_3$), 3.56 (br s, 1 H, C_3 H), 3.23 (br s, 1 H, C_4 H), 1.24 (t, *J* = 7 Hz, 3 H, $CO_2CH_2CH_3$), 0.84 (s, 9, H, *tert*-butyl).

Anal. Calcd for $C_{19}H_{28}O_4S$: C, 64.74; H, 8.01. Found: C, 64.83; H, 8.08.

Further elution gave the *r*-1, *c*-3, *c*-4 ester sulfone (**13**, 47 mg, 28%): mp 114.5–115 °C (aqueous ethanol), identical with the sample prepared as described below from the *r*-1, *c*-3, *c*-4 sulfone acid; ir (film) 1725 (C=O), 1305, 1150 cm^{-1} (SO_2); NMR ($CDCl_3$) δ 7.85, 7.55 (m, 5 H, ArH), 4.00 (m, **ABX**$_3$, 2 H, $CO_2CH_2CH_3$), 2.80 (m, 2 H, C_3 H and C_4 H), 1.20 (t, 3 H, $CO_2CH_2CH_3$), 0.90 (s, 9 H, *tert*-butyl).

Anal. Calcd for $C_{19}H_{28}O_4S$: C, 64.74; H, 8.01. Found: C, 65.00; H, 8.22.

When this oxidation was repeated using **4** (0.60 g), glacial acetic acid (15 ml), 30% hydrogen peroxide (0.9 ml), and concentrated sulfuric acid (1 drop) at room temperature, only **12** could be detected after 2 h and after 20.5 h. No explanation of the discrepancy is available at this time.

Ethyl *r*-1-*tert*-Butyl-*e*-3-phenylsulfonylcyclohexane-*c*-4-carboxamide. The *r*-1, c-3, c-4 sulfone nitrile[3] (1.17 g) and polyphosphoric acid (30 g) were heated at 80 °C for 3 h. The solution was poured into water (50 ml) and extracted with $CHCl_3$ (3 × 100 ml). The organic layer was dried ($MgSO_4$), concentrated (after decolorizing with charcoal), and triturated with light petroleum to give the amide sulfone (0.434 g, 38%): mp 192–193.5 °C (sublimation) (aqueous ethanol); ir (KBr) 3460, 3360 (NH_2), 1685 (C=O), 1605, 1280, 1150 cm^{-1}; NMR ($CDCl_3$) δ 7.90, 7.60 (m, 5 H, ArH), 4.10 (m, 2 H, C_4 H, C_3 H), 0.80 (s, 9 H, *tert*-butyl).

Anal. Calcd for $C_{17}H_{25}NO_3S$: C, 63.12; H, 8.44. Found: C, 63.22; H, 7.99.

***r*-1-*tert*-Butyl-*c*-3-phenylsulfonylcyclohexane-*c*-4-carboxylic Acid.** The above amide (0.123 g) in glacial acetic acid (3 ml), concentrated sulfuric acid (2.12 ml), and water (1.64 ml) at 3 °C was treated with sodium nitrite (0.10 g) with stirring. The white precipitate was stirred at 0 °C for 1 h and at room temperature for 12 h and water (20 ml) was then added. The mixture was extracted with ether (4 × 20 ml) and the dried ($MgSO_4$) combined extracts were evaporated to give the sulfone acid (0.102 g, 84%): mp 183–184 °C (from ether–light petroleum); ir (KBr) 3300–2400 (CO_2H), 1695 (C=O), 1305, 1140 cm^{-1} (SO_2).

Anal. Calcd for $C_{17}H_{24}O_4S$: C, 62.93; H, 7.46. Found: C, 62.77; H, 7.64.

Ethyl *r*-1-*tert*-Butyl-*c*-3-phenylsulfonylcyclohexane-*c*-4-carboxylate (13). The acid was esterified with ethanol and sulfuric acid to give the ester (29%), identical with the one obtained above in the oxidation and epimerization.

***r*-1-*tert*-Butyl-*c*-4-hydroxymethyl-*c*-3-phenylsulfonylcyclohexane (16).** The above *r*-1, *c*-3, *c*-4 sulfone acid (1.154 g) in dry ether (10 ml) was boiled under reflux for 6 h with a solution of $LiAlH_4$ (116 mg) in dry ether (10 ml). Careful addition of water followed by pouring the solution into 1 N HCl and extraction with ether gave the alcohol (**16**) as a yellow oil (0.56 g, 50%) which was purified by chromatography on a column of silica gel (50 g) and elution with benzene–$CHCl_3$ (1:1 v/v): ir (film) 3450 (OH), 1305, 1150 cm^{-1} (SO_2); NMR ($CDCl_3$) δ 7.95, 7.65 (m, 5 H, ArH), 3.80 (m, 3 H, **ABC**, $CHCH_2OH$), 3.10 (d of t, J_{aa} = 14, J_{ae} = 5 Hz, 1 H, C_3 H), 2.92 (s, 1 H, OH, exchange with D_2O), 0.88 (s, 9 H, *tert*-butyl).

Anal. Calcd for $C_{17}H_{26}O_3S$: C, 65.77; H, 8.44. Found: C, 65.63, H, 8.59.

***r*-1-*tert*-Butyl-*t*-4-hydroxymethyl-*t*-3-phenylsulfonylcyclohexane (14).** The ester **11** (1.85 g) in dry ether (30 ml) was treated with a solution of lithium aluminum hydride in ether (2 M, 3 ml) dropwise at such a rate as to maintain reflux. The solution was then stirred at room temperature for 2 h and excess hydride was decomposed with EtOH. Workup as above gave the alcohol **14** (1.63 g, 74%): mp 103–105 °C (from *n*-hexane); ir (CCl_4) 3530, 1308, 1145 cm^{-1}; NMR ($CDCl_3$) δ 7.90, 7.60 (m, 5 H, ArH), 4.20 (m, 3 H, CH_2OH and C_3 H), 3.07 (s, 1 H, OH, exchanges with D_2O), 0.69 (s, 9 H, *tert*-butyl).

Anal. Calcd for $C_{17}H_{26}O_3S$: C, 65.77; H, 8.44. Found: C, 65.61; H, 8.49.

***r*-1-*tert*-Butyl-*e*-4-hydroxymethyl-*t*-3-phenylsulfonylcyclohexane (15). A.** This was prepared from **12** by $LiAlH_4$ reduction as described above for **14**. The alcohol (68%) had bp 160 °C (0.007 mm) (dec); ir (CCl_4) 3450, 1310, 1150 cm^{-1}; NMR ($CDCl_3$) δ 7.90, 7.50 (m, 5 H, ArH), 4.20 (s, 1 H, OH exchangeable), 3.60 (m, 3 H, CH_2OH and C_3 H), 2.60 (s, 1 H, OH, exchangeable), 0.80 (s, 9 H, *tert*-butyl).

Anal. Calcd for $C_{17}H_{26}O_3S$: C, 65.77; H, 8.44. Found: C, 65.58; H, 8.49.

B. Oxidation of the *r*-1, *t*-3, *c*-4 alcohol sulfide[3] with peracetic acid solution initially gave the corresponding sulfone acetate [δ 1.92 (s, 3 H, CH_3CO_2)] which, following repeated attempts at recrystallization, gave the above alcohol.

Methyl *r*-1-*tert*-Butyl-*t*-3-thiophenoxycyclohexane-*t*-4-carboxylate. The acid **6** (1 g) was esterified with methanol (30 ml) and sulfuric acid (4 drops) to give the ester (0.96 g, 90%): mp 69–69.5 °C; ir (KBr) 1740 cm^{-1}; NMR (CCl_4) δ 7.30 (m, 5 H, ArH), 3.84 (q, J_{ae} = 4 Hz, 1 H, C_3 H), 3.42 (s, 3 H, CO_2CH_3), 2.60 (d of t, J_{aa} = 10, J_{ae} = 4 Hz, 1 H, C_4 H), 0.84 (s, 9 H, *tert*-butyl).

Anal. Calcd for $C_{18}H_{26}C_2S$: C, 70.75; H, 8.55. Found: C, 70.51; H, 8.68.

Methyl *r*-1-*tert*-Butyl-*t*-3-phenylsulfonylcyclohexane-*t*-4-carboxylate (18). The above ester (0.618 g) in glacial acetic acid (25 ml) containing 30% hydrogen peroxide (1.5 ml) and concentrated H_2SO_4 (2 drops) was stirred at room temperature for 3 h. The solvent was evaporated and the sulfone **18** (0.68 g, 100%) was recrystallized from aqueous ethanol: mp 143–143.5 °C; ir (KBr) 1740, 1305, 1140 cm^{-1}; NMR ($CDCl_3$) δ 7.85, 7.55 (m, 5 H, ArH), 3.82 (br s, 1 H, C_3 H), 3.54 (s, 3 H, CO_2CH_3), 2.50 (d of t, 1 H, C_4 H), 0.80 (s, 9 H, *tert*-butyl).

Anal. Calcd for $C_{18}H_{26}O_4S$: C, 63.87; H, 7.74. Found: C, 64.01; H, 7.83.

***r*-1-*tert*-Butyl-*t*-3-phenylsulfonylcyclohexane-*t*-4-carboxylic Acid (17).** Sulfide **6** was oxidized in the same manner as was ester **18** to give the sulfone **17** (100%): mp 160 °C (sublimation); ir (KBr) 3300–2500 (br), 1720, 1300, 1140 cm^{-1}; NMR ($CDCl_3$) δ 9.26 (br s, 1 H, CO_2H, exchangeable), 7.90, 7.60 (m, 5 H, ArH), 3.95 (br s, 1 H, C_3

H), 2.60 (d of t, J_{aa} = 11, J_{ae} = 4 Hz, 1 H, C_4 H), 0.80 (s, 9 H, *tert*-butyl).

Anal. Calcd for $C_{17}H_{24}O_4S$: C, 62.93; H, 7.46. Found: C, 62.83; H, 7.66.

Dispiro[bis(4-*tert*-butylcyclohexane-1,2',5',1''-oxazolid-4'-one)] (20). 4-*tert*-Butylcyclohexanone cyanohydrin (**19**, 2 g) was dissolved in a mixture of 95% EtOH (5 ml) and concentrated HCl (5 ml). The solution was boiled under reflux for 13 h. The precipitated oxazolidone (0.20 g, 9%) was filtered and had mp 330 °C; ir 3400, 3290, 1685 (C=O), 1090 cm^{-1}; the NMR spectrum could not be determined owing to the insolubility of this compound in the usual solvents; mass spectrum (70 eV) *m/e* (rel intensity) 336 (0.8), 335 ($M^{\cdot+}$, 2.4), 320 (2.6) 236 (100), 182 (3.4), 180 (4.6), 164 (70), 154 (9.2), 138 (9.2).

Anal. Calcd for $C_{21}H_{37}NO_2$: C, 75.17; H, 11.12; N, 4.18. Found: C, 75.55; H, 11.14; N, 4.23.

The same compound (identical ir spectra) could be obtained, albeit in even lower yield (3.5%), by keeping a mixture of the cyanohydrin and polyphosphoric acid at room temperature.[13]

Acknowledgments. Part of this work was carried out during the tenure (by S.S.S.) of an NDEA Fellowship (1970–1971). Thanks are due to the Dow Chemical Co. for the gift of 4-*tert*-butylcyclohexanone.

Registry No.—**1**, 23022-33-5; **9**, 35905-86-3; **10**, 58463-38-0; **10** 4-c isomer, 58463-39-1; **11**, 58463-32-4; **12**, 58463-40-4; **13**, 58463-41-5; **14**, 58463-42-6; **15**, 58463-43-7; **16**, 58463-44-8; **17**, 58463-45-9; **18**, 58463-46-0; **19**, 941-44-6; **20**, 58463-47-1; ethyl *r*-1-*tert*-butyl-*c*-3-phenylsulfonylcyclohexane-*c*-4-carboxamide, 58463-48-2; *r*-1-*tert*-butyl-*c*-3-phenylsulfonylcyclohexane-*c*-4-carbonitrile, 35905-99-8; *r*-1-*tert*-butyl-*c*-3-phenylsulfonylcyclohexane-*c*-4-carboxylic acid, 58463-49-3; methyl 1-*r*-*tert*-butyl-*t*-3-thiophenoxycyclohexane-*t*-4-carboxylate, 58463-50-6; thiophenol, 108-98-5.

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(6) Equilibration appears to occur, at least partly, via retro-Michael addition followed by readdition.[3] The isolation of olefin **1** from some equilibration experiments supports this suggestion. Since elimination from **4** would be expected to be more difficult than from **5** this could explain slight differences observed between the ratio obtained starting from pure **5** and from the addition under thermodynamic control conditions, and also the different ratio obtained in the dipolar aprotic solvent, DMF, used.[1]
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Reaction of Pyridine 1-Oxides and *N*-Iminopyridinium Ylides with Diazonium Salts. *N*-Aryloxypyridinium Salts and Their Base-Catalyzed Rearrangement

Rudolph A. Abramovitch,* Muthiah N. Inbasekaran, Shozo Kato, and George M. Singer

Department of Chemistry, University of Alabama, University, Alabama 35486

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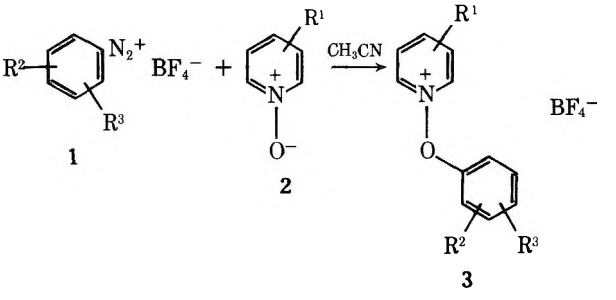
N-Aryloxypyridinium tetrafluoroborates are prepared by the reaction of pyridine 1-oxides with aryldiazonium tetrafluoroborates bearing an electron-withdrawing substituent in the aryl ring. The scope, limitations, and possible mechanism of the reaction are discussed. The salts undergo base-catalyzed rearrangement to give 2-*o*-hydroxyarylpyridines. *N*-Aminopyridinium tetrafluoroborates react with aromatic diazonium salts in acetonitrile to give 1-[(*N*-arylacetimidoyl)amino]pyridinium tetrafluoroborates (**14**) but no *N*-arylaminopyridinium tetrafluoroborates. Related compounds are formed in propionitrile and malononitrile, but not in butyronitrile and benzonitrile. In butyronitrile, for example, 1-(*N*-butyrimidoylamino)iminopyridinium tetrafluoroborate (**16**) is formed. Compounds **14** give the corresponding ylides with base. Treatment of *N*-aryliminopyridinium ylides with base does not lead to their rearrangement to 2-*o*-aminoarylpyridines.

N-Alkoxypyridinium salts are well-known compounds whose preparation[1] and properties[1,2] have recently been reviewed. They are usually readily made from the *N*-oxide and an alkyl halide, dialkyl sulfate, or alkyl sulfonate. In contrast, the *N*-aryloxy compounds were not known when this work was initiated.[3] Attempts to phenylate pyridine 1-oxide with diphenyliodonium bromide or benzenediazonium tetrafluoroborate failed.[4] We now report[3] a convenient synthesis of such compounds and a novel molecular rearrangement which they undergo.

It was expected that, for a direct arylation to occur between a diazonium salt and an *N*-oxide, the salt would have to be more electrophilic than unsubstituted benzenediazonium tetrafluoroborate, rather than going the other way and making the *N*-oxide more nucleophilic. It was felt that if the latter were the case the *N*-oxide might induce a homolytic decomposition via the diazo compound[5] which would defeat the purpose. To this end, the diazonium tetrafluoroborate (**1**) of



an aromatic amine bearing an electron-withdrawing substituent was added to a solution of a pyridine 1-oxide (**2**) in acetonitrile and the solution was either stirred at room temperature or warmed gently to give the desired *N*-aryloxypyridinium tetrafluoroborate (**3**). The salts so prepared are listed in Table I.

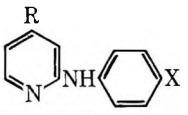
The structures of the salts **3** were established by spectro-

Table I. 1-Aryloxypyridinium Tetrafluoroborates (3)[g]

Registry no.	R^1	R^2	R^3	% yield	Mp, °C	Molecular formula
33393-61-2	H	4-NO_2	H	75	157.5–159	$C_{11}H_9BF_4N_2O_3$
33393-60-1	H	4-CN	H	70	214–215	$C_{12}H_9BF_4N_2O$
33393-59-8	H	4-CF_3	H	36	135–136	$C_{12}H_9BF_7NO$
33395-25-4	H	3-NO_2	H	24	149–150	$C_{11}H_9BF_4N_2O_3$
33395-26-5	H	2-NO_2	H	27	161–162	$C_{11}H_9BF_4N_2O_3$
33395-27-6	H	2-CF_3	H	44	169–170	$C_{12}H_9BF_7NO$
55165-47-4	H	2-CN	H	19	160.5–162	$C_{12}H_9BF_4N_2O$
58408-63-2	H[a,b]	2-NO_2	4-NO_2	86	182–184	$C_{11}H_8BF_4N_3O_5$
58408-65-4	H[b]	3-NO_2	5-NO_2	56	190–192	$C_{11}H_8BF_4N_3O_5$
58408-67-6	4-CH_3	4-NO_2	H	22	136–137	$C_{12}H_{11}BF_4N_2O_3$
58408-69-8	4-CH_3	4-CN	H	37	177–179	$C_{13}H_{11}BF_4N_2O$
58408-71-2	4-CH_3	2-NO_2	H	34	147–148	$C_{12}H_{11}BF_4N_2O_3$
58408-73-4	4-C_6H_5	4-CN	H	75	193–194	$C_{18}H_{13}BF_4N_2O$
58408-75-6	4-C_6H_5	4-NO_2	H	87	188–189	$C_{17}H_{13}BF_4N_2O_3$
58408-77-8	4-OCH_3	4-NO_2	H	61	151.5–153	$C_{12}H_{11}BF_4N_2O_4$
58408-79-0	4-OC_6H_5	4-NO_2	H	59	209–211	$C_{17}H_{13}BF_4N_2O_4$
58408-81-4	4-Cl[d]	4-NO_2	H	64	170	$C_{11}H_8BClF_4N_2O_3$
58408-83-6	4-CN[e]	4-CN	H	5	166–167	$C_{13}H_8BF_4N_3O$
58408-85-8	2-OCH_3	4-NO_2	H	87	168.5–170	$C_{12}H_{11}BF_4N_2O_4$
58408-87-0	4-OCH_3[f]	2-NO_2	4-NO_2	71	125–127	$C_{12}H_{10}BF_4N_3O_6$
58408-89-2	4-CN[b]	2-NO_2	4-NO_2	84	208–209	$C_{12}H_7BF_4N_4O_5$
58408-91-6	4-[b]	2-NO_2	4-NO_2	77	217–218.5 dec	$C_{22}H_{14}B_2F_8N_6O_{10}$

[a] Isolated as the perchlorate, a rather explosive compound. [b] Sulfolane was used as the reaction solvent, while acetonitrile was the solvent in other cases. [c] Also from the 4-chloro derivative by repeated recrystallization from methanol. [d] 4-Chloro-2-*p*-nitroanilinopyridine (7%) was also isolated. [e] 4-Cyano-2-*p*-cyanoanilinopyridine (29%) was also isolated (see Experimental Section). [f] Could not be purified because of its slow rearrangement to **6** on recrystallization. [g] Satisfactory analytical data (±0.3% for C, H) were reported for all compounds except the 4-methoxyphenyl derivative. Ed.

Table II. 2-Anilinopyridines[a]

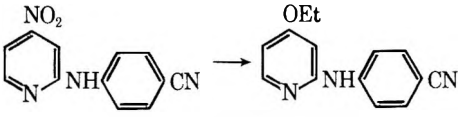


Registry no.	R	X	% yield	Mp, °C	Molecular formula
58408-92-7	NO_2	CN	29	222–224	$C_{12}H_8N_4O_2$
58408-93-8	CN	CN	29	238–240	$C_{13}H_8N_4$
58408-94-9	CN	NO_2	12	243–244	$C_{12}H_8N_4O_2$
58408-95-0	CN	CF_3	44	184–186	$C_{13}H_8N_3F_3$
58408-96-1	NO_2	CF_3	27	162–163.5	$C_{12}H_8F_3N_3O_2$
58408-97-2	NO_2	NO_2	20	264–267	$C_{11}H_8N_4O_4$
58408-98-3	Cl	NO_2	9	201–204	$C_{11}H_8N_3O_2Cl$
58408-99-4	Cl	CN	15	206–208	$C_{12}H_8N_3Cl$

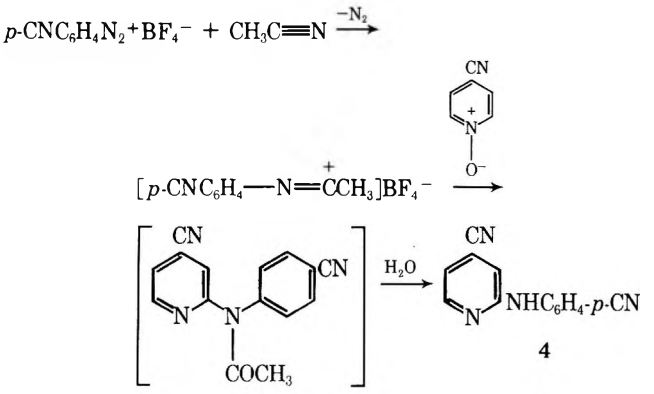
[a] Satisfactory analyses (±0.3% for C, H) were reported for all compounds in table. Ed.

scopic methods and by microanalysis. In particular, the NMR spectra indicated that arylation had occurred at oxygen. For example, 1-(4-nitrohenoxy)pyridinium tetrafluoroborate (**3**, $R^1 = R^3 = H$; $R^2 = p$-NO_2) exhibited bands at δ 9.65 (2 H, d, $J_{2,3} = J_{5,6} = 6$ Hz, H-2,6), 9.00 (1 H, t, $J_{3,4} = J_{4,5} = 7$ Hz, H_4), 8.56 (2 H, d of d, H-3,5), 8.39 (2 H, d, $J_o = 9$ Hz, phenyl meta hydrogens), and 7.50 (2 H, d, $J_o = 9$ Hz, phenyl ortho hydrogens).

The most notable failure of this arylation occurred with 4-nitro- and 2-methylpyridine 1-oxides. The *N*-oxide function in 4-nitropyridine 1-oxide is, presumably, not basic enough to react with the diazonium ion (what may be an impure form of the desired salt was isolated). Some 2-(*p*-nitroanilino)-4-nitropyridine was formed. Arylation of 4-nitro- and 4-cyanopyridine 1-oxides in acetonitrile with other diazonium salts gave only the corresponding 2-anilinopyridines and these results are collected in Table II. The nitro group in 2-(*p*-cyanoanilino)-4-nitropyridine underwent the expected displacement with ethoxide ion. An intermediate situation was observed with the somewhat more basic 4-cyanopyridine 1-oxide in acetonitrile solution, using *p*-cyanobenzenediazonium tetrafluoroborate as the arylating agent. A low (5%) yield of



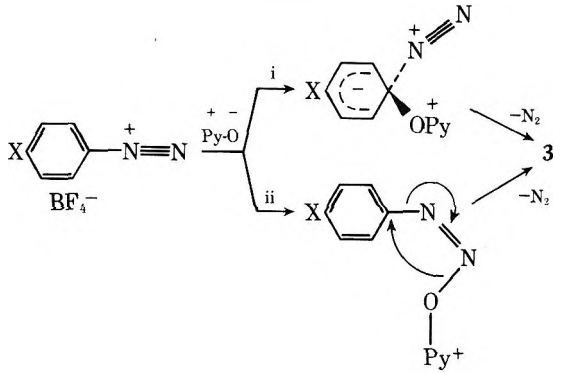
the desired salt (**3**, R^1 = 4-CN; R^2 = 4-CN; R^3 = H) was obtained, together with a 29% yield of 2-(*p*-cyanoanilino)-4-cyanopyridine (**4**). The latter was presumably formed by the hydrolysis of the initially formed acetamide (**5**).[6]



A similar situation was found with 4-chloropyridine 1-oxide. Reaction with *p*-nitrobenzenediazonium tetrafluoroborate in acetonitrile gave a mixture of **3** (R^1 = 4-Cl; R^2 = 4-NO_2; R^3 = H) and 4-chloro-2-*p*-nitroanilinopyridine (7%). Attempted purification of the pyridinium salt from hot methanol led to a mixture of the 4-chloro- and 4-methoxypyridinium derivatives. More prolonged heating with methanol led to complete nucleophilic displacement of the chlorine atom and the formation of **3** (R^1 = 4-OMe; R^2 = 4-NO_2; R^3 = H). When *p*-cyanobenzenediazonium tetrafluoroborate was used, 4-chloro-2-*p*-cyanoanilinopyridine could be obtained pure following methanolic workup, together with a mixture of the corresponding 4-chloro- and 4-methoxypyridinium salts. No attempt was made to separate these.

4,4′-Bipyridyl 1,1′-dioxide was not arylated by *p*-nitro-

Scheme I

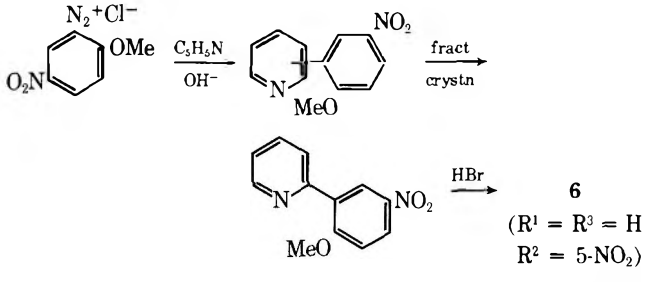


benzenediazonium tetrafluoroborate, probably because it was not basic enough, but was arylated in good yield (Table I) by using the more electrophilic 2,4-dinitrobenzenediazonium tetrafluoroborate in sulfolane solution (to avoid nitrilium ion formation in acetonitrile with the more electrophilic cation); other examples are given in Table I.

2-Picoline 1-oxide was not O-arylated and it is hard to imagine that the *N*-oxide function would be sufficiently sterically hindered by the 2 substituent to prevent attack, but no alternate explanation can be advanced at this time (vide infra).

The O-arylations occur at temperatures (usually room temperature) well below those at which unimolecular decomposition of the diazonium salts occur. Indeed, in the absence of *N*-oxide, the diazonium salts are stable in solution under these conditions. This suggests either that an SNAr displacement (path i) (or a direct SN2 process) is taking place[7] or that a diazo oxide is first formed which collapses to **3** with loss of nitrogen (path ii) (Scheme I).

Pyridine 1-oxides and pyridinium salts undergo base-catalyzed proton abstraction from the 2 position of the pyridine ring.[8] Treatment of the salts **3** in hot acetonitrile solution either with potassium phenoxide or with triethylamine gave the corresponding 2-(2-hydroxyaryl)pyridine (**6**). For example, **3** ($R^1 = R^3 = H$; $R^2 = 4\text{-}NO_2$) gave **6** ($R^1 = R^3 = H$, $5\text{-}NO_2$)

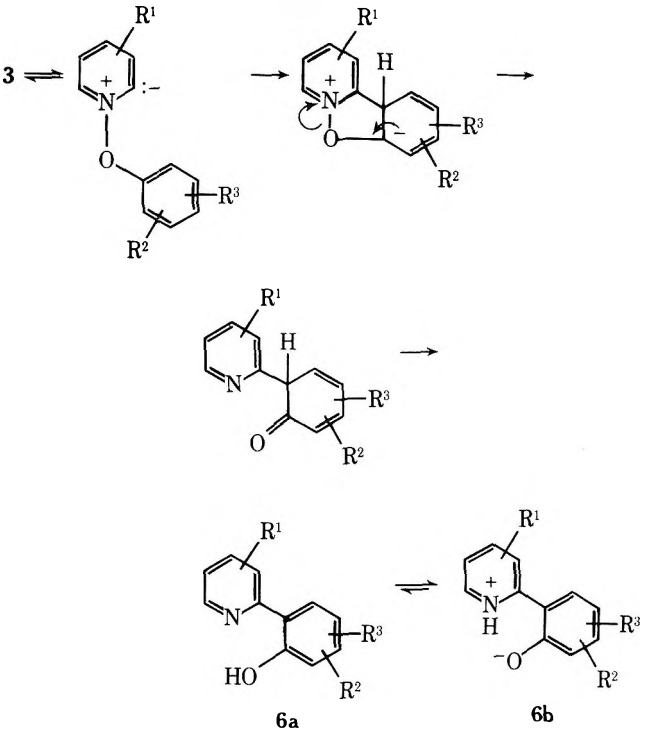


whose structure was established by its spectral properties and by its synthesis by an unambiguous route. Thus, Gomberg–Hey arylation of pyridine with the diazonium salt from 2-amino-4-nitroanisole gave a mixture of the three possible arylation products which were fractionally crystallized to give 2-(2-methoxy-5-nitrophenyl)pyridine.[9] This was demethylated with hydrobromic acid to give authentic 2-(2-hydroxy-5-nitrophenyl)pyridine (**6**), identical with the compound obtained above. The spectral properties of the other rearrangement products **6** permitted unambiguous assignment of their structure. A possible mechanism for the base-catalyzed rearrangement is given in Scheme II.

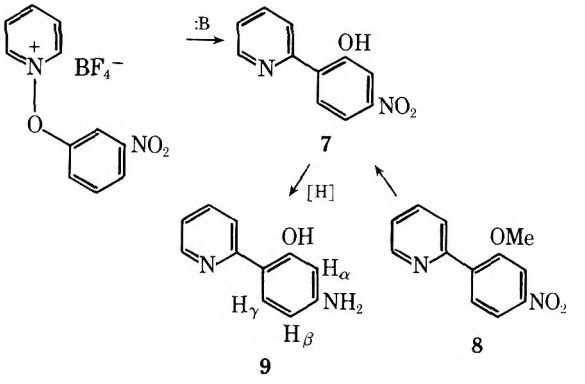
The phenols **6** do not exhibit an O–H stretching band in the infrared (or only a very weak broad band) either in the solid state or in solution, but do show a broad $-^+NH=$ band at ca. 2600 cm^{-1}, indicating that they exist mainly in the zwitterionic form **6b**.

The base-catalyzed rearrangement of 1-(3-nitrophenoxy)pyridinium tetrafluoroborate (**3**, $R^1 = R^3 = H$; $R^2 = 3\text{-}NO_2$) can, in principle, lead to two isomeric 2-*o*-hydroxyphenylpyridines via attack either ortho or para to the nitro group. In practice, only one product was obtained, namely **7** resulting from attack at the sterically less hindered para position. The NMR spectrum of the product could not be used to distinguish between the two possibilities as the protons on the nitrophenyl ring appeared as a broad singlet, probably owing to the compensating effects on the chemical shifts by the nitro and hydroxyl groups meta to each other. The rearranged product was reduced to the corresponding primary amine (**9**). This exhibited a narrow one-proton doublet ($J_{\alpha,\beta}$ = 2 Hz) at δ 6.57 (H_α), a 1 H quartet ($J_{\beta,\gamma}$ = 9.0, $J_{\alpha,\beta}$ = 2 Hz) at δ 6.66 (H_β), and a 1 H doublet ($J_{\beta,\gamma}$ = 9.0 Hz) at δ 8.07 (H_γ), clearly eliminating the alternate possibility which would have vicinal protons. This proposed structure was confirmed by the synthesis of authentic **7** by demethylation of 2-(2-methoxy-4-nitrophenyl)pyridine (**8**).

Scheme II



6a **6b**



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The yield of rearranged product from 4-methyl-1-(4-nitrophenoxy)pyridinium tetrafluoroborate (**3**, R^1 = 4-Me; $R^2 = 4\text{-}NO_2$; R^3 = H) was exceptionally low (9.6%). It is possible that base-catalyzed proton abstraction occurs from the methyl side chain which could lead to elimination of *p*-nitrophenol, as is observed. The pyridine-containing fragment was not isolated. The results of the base-catalyzed rearrangements are summarized in Table III. The phenols could be brominated readily, e.g., 2-(5-cyano-2-hydroxyphenyl)pyridine gave 2-

Table III. 2-(2-Hydroxyaryl)pyridines (6)

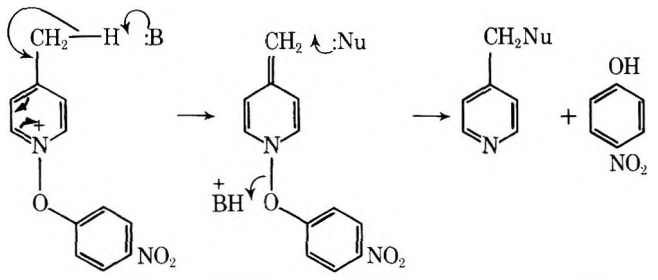
Registry no.	R^1	R^2	R^3	% yield	Mp, °C	Molecular formula
33400-82-7	H	5-NO_2	H	65	216–217	$C_{11}H_8N_2O_3$
33400-78-1	H	3-NO_2	H	66	167–168	$C_{11}H_8N_2O_3$
58409-00-0	H	4-NO_2[a]	H	33	186.5–187.5	$C_{11}H_8N_2O_3$
33400-81-6	H	5-CN	H	69	198–199	$C_{12}H_8N_2O$
33400-80-5	H	5-CF_3	H	40	92–93	$C_{12}H_8F_3NO$
33400-79-2	H	3-CF_3	H	49	87–88	$C_{12}H_8F_3NO$
55165-48-5	H	3-CN	H	28	180–182	$C_{12}H_8N_2O$
58409-01-1	4-C_6H_5	5-CN	H	53	164.5–165.5	$C_{18}H_{12}N_2O$
58409-02-2	4-CH_3[b]	5-NO_2	H	10	204–205.5	$C_{12}H_{10}N_2O_3$
58409-03-3	4-OCH_3	5-NO_2	H	68	191.5–192.5	$C_{12}H_{10}N_2O_4$
58409-04-4	4-OC_6H_5	5-NO_2	H	81	147–148	$C_{17}H_{12}N_2O_4$
58409-05-5	4-OCH_3	3-NO_2	5-NO_2	69	289–291 dec	$C_{12}H_9N_3O_6$

[a] From 3 (R^2 = 3-NO_2). [b] *p*-Nitrophenol was the major product (49.7%). [c] Satisfactory analyses (±0.3% for C, H) were reported for all compounds in table. Ed.

Table IV. 1-[(*N*-Arylacetimidoyl)amino]pyridinium Tetrafluoroborates (14)[a]

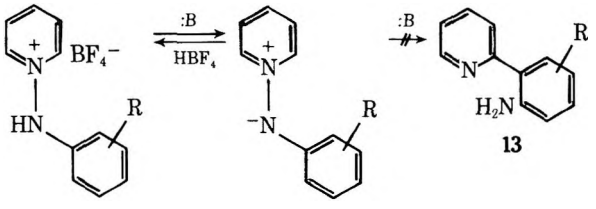
Registry no.	R	X	% yield	Mp, °C	Molecular formula
58409-07-7	H	4-CN	54	282–283	$C_{14}H_{13}BF_4N_4$
58409-09-9	H	4-NO_2	40	268–270	$C_{13}H_{13}BF_4N_4O_2$
58409-11-3	H	4-CF_3	58	253–255	$C_{14}H_{13}BF_7N_3$
58409-13-5	H	3-Cl	45	190–192	$C_{13}H_{13}BClF_4N_3$
58409-15-7	H	H	52	202–204	$C_{13}H_{14}BF_4N_3$
58409-17-9	H	3-NO_2	40.5	155–156	$C_{13}H_{13}BF_4N_4O_2$
58409-19-1	H	4-Cl	30	217–218.5	$C_{13}H_{13}BClF_4N_3$
58409-21-5	2-CH_3	4-CN	38	210–211	$C_{15}H_{15}BF_4N_4$
58409-23-7	2-CH_3	H	38	239–240	$C_{14}H_{16}BF_4N_3$
58409-25-9	3,5-Me_2	4-NO_2	77	262–266	$C_{15}H_{17}BF_6O_2$
58409-27-1	3,5-Me_2	3-Cl	41	254–255	$C_{15}H_{17}BClF_4N_3$
58409-29-3	2,6-Me_2	3-Cl	49	228–229	$C_{15}H_{17}BClF_4N_3$

[a] Satisfactory analytical values (±0.3% for C, H) were reported for all compounds. Ed.



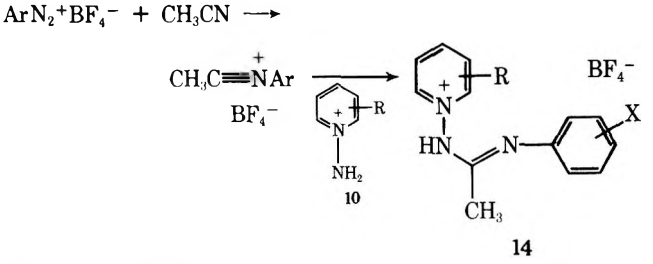
(3-bromo-5-cyano-2-hydroxyphenyl)pyridine with bromine in acetic acid.

The above reactions thus provide convenient routes to both *N*-aryloxypyridinium salts and, via a new molecular rearrangement, to 2-o-hydroxyphenylpyridine derivatives. It was of considerable interest, therefore, to see if these reactions could be extended to the N-arylation of either 1-aminopyridinium salts [$RC_5H_4{}^+NNH_2$] BF_4^- (**10**) or of the corresponding 1-imino ylide $RC_5H_4N^+N^-H$ (**11**) to give *N*-arylaminopyridinium salts (**12**). It was also of interest to determine whether these, if formed, would undergo base-catalyzed rearrangement to the corresponding 2-o-aminophenylpyridines (**13**) which are difficult to prepare by conventional routes. In contrast to the *N*-aryloxypyridinium salts, the pyridine *N*-phenylimines are known compounds[10,11] and, indeed, N-arylation of **10** has been achieved using an activated aryl halide.[12]



12 13

The reaction of 1-aminopyridinium tetrafluoroborates (**10**) with aryldiazonium tetrafluoroborates (bearing electron-withdrawing groups in the aryl ring) in acetonitrile solution did not yield any of the desired *N*-aryliminopyridinium salts (**12**). The only products isolated were the 1-[(*N*-arylacetimidoyl)amino]pyridinium tetrafluoroborates (**14**) (Table IV).



10 14

These are probably formed via the nitrilium ion resulting from the N-arylation of solvent acetonitrile followed by attack at the *N*-amino group. It is interesting that in these cases, as opposed to the *N*-oxide situation, reaction does occur at nitrogen in the 2-picoline derivative. There is, therefore, no apparent undue steric hindrance by a 2-methyl group to attack by a carbenium ion at the *N*-imino nitrogen atom, which would suggest that in the arylations at oxygen, path i (Scheme I), may be operating in the formation of **3**, since much more steric hindrance would be anticipated in this pathway than in path ii.

When the reactions were carried out in propionitrile or malononitrile the corresponding 1-[(*N*-arylimidoyl)amino]pyridinium tetrafluoroborates (**15**) were usually obtained, though the yields were rather poor (Table V). Butyronitrile appeared to be an exception. When 1-aminopyridinium tetrafluoroborate in butyronitrile was treated either with *p*-nitro- or *p*-trifluoromethylbenzenediazonium tetrafluoroborate no **15** was formed. Instead, the same product was obtained in each

Table V. Products (15) of Reaction of 1-Aminopyridinium Tetrafluoroborates with Aryldiazonium Tetrafluoroborates in Various Nitriles[d]

Solvent	Registry no.	R¹	X	R²	% yield	Mp, °C	Molecular formula
Propionitrile	58409-31-7	H	4-CNC_6H_5	CH_3CH_2	23	206–207	$C_{15}H_{15}BF_4N_4$
Propionitrile	58409-33-9	H	4-$NO_2C_6H_5$	CH_3CH_2	31.5	200–201	$C_{14}H_{15}BF_4N_4O_2$
Propionitrile	58425-88-0	3,5-Me_2	4-$NO_2C_6H_5$	CH_3CH_2	20	187–188	$C_{16}H_{19}BF_4N_4O_2$
Malononitrile	58425-90-4	H[a]	4-$NO_2C_6H_5$	N≡C–CH_2	57	187–188	$C_{14}H_{12}BF_4N_5O_2$
Butyronitrile	58548-79-1	H[b]	H	$CH_3CH_2CH_2$	28	159–160	$C_9H_{14}BF_4N_3$
Benzonitrile	58425-92-6	H[c]	H	C_6H_5	9	178–179	$C_{12}H_{12}BF_4N_3$

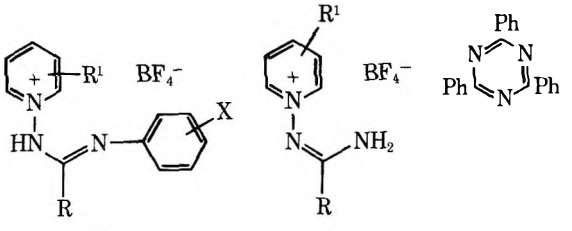
[a] ω-Cyano-*p*-nitroacetanilide (9%) was also isolated. [b] From *p*-nitro- or *p*-trifluoromethylbenzenediazonium tetrafluoroborate. A small amount of 2,4,6-triphenyl-*s*-triazine was also isolated. [c] From *p*-nitrobenzenediazonium tetrafluoroborate. [d] Satisfactory analytical values were reported for all compounds in Table. Ed.

Table VI. 1-[(*N*-Arylacetimidoyl)imino]pyridinium Ylides (19)[a]

Registry no.	R	X	% yield	Mp, °C	Molecular formula
58425-93-7	H	4-NO_2	71.5	157–159	$C_{13}H_{12}N_4O_2$
58425-94-8	H	4-CN	67	159–160	$C_{14}H_{12}N_4$
58425-95-9	3,5-Me_2	4-NO_2	72	136–137	$C_{15}H_{16}N_4O_2$

[a] Satisfactory analytical values (±0.3%) were reported for all compounds in Table . Ed.

case, whose spectral properties and analysis showed it to be the salt **16** (R = *n*-Pr; R^1 = H). In the reaction with the *p*-nitrodiazonium salt some *p*-nitrobutyranilide was also obtained. No reaction occurred between 1-aminopyridinium tetrafluoroborates and butyronitrile in the absence of diazonium salt. A similar product (12.5%) was obtained from 1-aminopyridinium tetrafluoroborate and *p*-trifluoromethylbenzenediazonium tetrafluoroborate (but not from the *p*-nitrodiazonium salt) in boiling propionitrile. Unfortunately, it could not be obtained analytically pure. A low (9%) yield of **16** (R = Ph; R^1 = H) was obtained from the amine, *p*-nitrobenzenediazonium tetrafluoroborate, and benzonitrile, together with small amounts of 2,4,6-triphenyl-*s*-triazine (**17**).

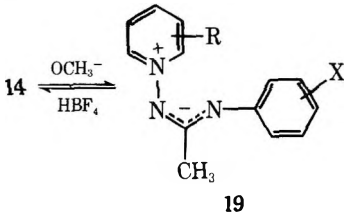


15 **16** **17**

The latter was also isolated when *p*-cyano- and *p*-trifluoromethylbenzenediazonium tetrafluoroborate were used. These reactions may be rationalized if it is assumed that decomposition of the diazonium tetrafluoroborates in the higher boiling solvents gives some boron trifluoride (via the Schiemann reaction) which now reacts with the nitriles to give a nitrilium salt that attacks the *N*-aminopyridinium salt. Acid-catalyzed trimerization of benzonitrile to **17** is known.[13a]

$$R{-}C{\equiv}N + BF_3 \rightleftharpoons R{-}C{=}N{-}BF_3 \xrightarrow{H_2NR^1} \mathbf{16}$$

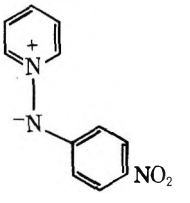
Treatment of the salts **14** with base such as sodium methoxide gave the ylide **19** (Table VI) which was converted back to **14** on acidification. The conjugate acid of **19** was also formed on treatment of **19** with aqueous silver nitrate, or dimethyl sulfate in benzene, or acetyl chloride in benzene.



19

The reaction of diazonium tetrafluoroborates with *N*-aminopyridinium tetrafluoroborate was attempted in dioxane to avoid the participation of nitrile solvents. None of the desired product could be obtained. In order to make the substrate more nucleophilic so that it could compete more effectively with acetonitrile solvent for the electrophilic reagent the *N*-iminopyridinium ylide (from the *N*-amino compound and sodium carbonate or sodium hydride) in acetonitrile was treated with diazonium tetrafluoroborate. The only product formed was the corresponding aryl azide (25–52%) and starting aminopyridinium salt was recovered (75–15%). Similar behavior has been reported[13b] for reactions in aqueous medium.

Since an *N*-arylaminopyridinium salt could not be obtained in this way, a modification of Okamoto's method[12] was used to prepare pyridine-*N*-(4-nitrophenyl)imine (**20**). Pyridine 1-oxide is known to give the corresponding α anion with sodium hydride.[14] When **20** was heated with sodium hydride in acetonitrile the solution turned from red to black, but the black solid did not yield any of the desired amine (**13**, R =



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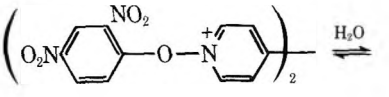
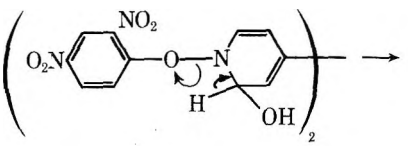
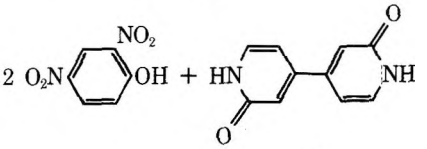


$2BF_4^-$

21





22

4-NO_2), only **20** being recovered (47%). Compound **20** was also recovered quantitatively on heating with lithium diethylamide. Thus, the base-catalyzed rearrangement of **20** to **13** has not been achieved yet.

1,1′-Di(2,4-dinitrophenoxy)-4,4′-dipyridylium ditetrafluoroborate (**21**) did not give the corresponding *o*-hydroxyarylpyridine with base. Heating in boiling water led to the elimination of 2,4-dinitrophenol and the formation of 4,4′-di(2-pyridone) (**22**). Treatment of **21** with triethylamine in nitromethane gave only 2,4-dinitrophenol (31.5%) and unidentified tarry material.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded on a Varian Associates Model HA-100 or Perkin-Elmer Model R-20B spectrometer. Mass spectra were determined on a C. E. C. Model 21-104 spectrometer at an ionizing voltage of 70 eV. Infrared spectra were recorded on a Perkin-Elmer Model 257 instrument.

Reagents and Solvents. Acetonitrile was dried and distilled over calcium hydride. Sulfolane was distilled under vacuum just prior to use. Pyridine 1-oxides were purified by vacuum distillation or recrystallization and kept in a desiccator. Aryldiazonium tetrafluoroborates were prepared according to the standard procedure.[15]

O-Arylations. The general procedures used for the O-arylations using acetonitrile or sulfolane as the solvent are illustrated using specific examples. The products (**3**) so obtained are listed in Table I, as are the analytical data for new compounds.

Acetonitrile Solvent. 1-(4-Cyanophenoxy)pyridinium Tetrafluoroborate. *p*-Cyanobenzenediazonium tetrafluoroborate (2.17 g, 0.01 mol) was added portionwise to an ice-cold solution of pyridine 1-oxide (1.14 g, 0.012 mol) in dry acetonitrile (30 ml) with vigorous stirring. Rapid gas evolution accompanied the slightly exothermic reaction. The mixture turned dark red on stirring for 24 h at room temperature (or on heating under reflux for 4 h). The solvent was evaporated and the residue was recrystallized from methanol to give the salt (1.98 g, 70%): mp 214–215 °C; ir (KBr) 2240 (C≡N), 1130–1030 cm^{-1} (BF_4^-); NMR (Me_2SO-d_6) δ 9.96 (d, 2 H, $J_{\alpha\beta}$ = 7 Hz, H_α), 9.13 (t, 1 H, $J_{\beta\gamma}$ = 7 Hz, H_γ), 8.71 (t, 2 H, $J_{\alpha\beta} = J_{\beta\gamma}$ = 7 Hz, H_β), 8.32 (d, 2 H, $J_{o,m}$ = 9 Hz, H_o), and 7.67 (d, 2 H, $J_{o,m}$ = 9 Hz, H_m); mass spectrum *m/e* 244 ($M^{\cdot+}$ − 2HF, 12), 196 ($M^{\cdot+}$ − HBF_4, 9), 119 ($CNC_6H_4OH^{\cdot+}$, 57), 79 ($C_5H_5N^{\cdot+}$, 100), 52 (65), 49 (54).

Sulfolane Solvent. 1,1′-Di(2,4-dinitrophenoxy)-4,4′-dipyridylium Ditetrafluoroborate (21). *To a suspension of 4,4′-dipyridyl* 1,1′-dioxide (1.88 g, 0.01 mol) in sulfolane (8 ml) at 40–45 °C was added 2,4-dinitrobenzenediazonium tetrafluoroborate (5.92 g, 0.021 mol) slowly with stirring over 30 min. Stirring at 40–45 °C was continued for a further 1 h while nitrogen was evolved. Trituration with benzene–ether (1:3 v/v, 30 ml) and then with warm methanol (15 ml) gave a yellow solid (6.80 g, 97.8%) which, on recrystallization from nitromethane–acetic acid (4:1 v/v), gave the salt (5.38 g, 77.8%): mp 217–218.5° dec; ir (KBr) 1535, 1335 (NO_2), 1100–1000 cm^{-1} (BF_4^-); NMR (CH_3NO_2) δ 9.51 (d, 4 H, $J_{\alpha\beta}$ = 7 Hz, H_α), 9.10 (d, 2 H, J_{AB} = 2.5 Hz, H_A), 8.86 (d, 4 H, $J_{\alpha\beta}$ = 7 Hz, H_β), 8.61 (dd, 2 H, J_{BC} = 9, J_{AB} = 2.5 Hz, H_B), and 7.39 (d. 2 H, J_{BC} = 9 Hz, H_C); mass spectrum *m/e* 183 ($C_6H_3N_2O_5^+$, 80), 156 ($C_{10}H_8N_2^{\cdot+}$, 100).

2-(*p*-Cyanoanilino)-4-nitropyridine. A solution of 4-nitropyridine 1-oxide (1.40 g) and *p*-cyanobenzenediazonium tetrafluoroborate (2.17 g) in acetonitrile (20 ml) was boiled under reflux for 1 h. The solvent was evaporated to dryness to give a tarry residue which solidified on standing overnight. The solid was dissolved in methanol (45 ml), the insoluble tars were filtered, and the filtrate was kept in the refrigerator when **2-(*p*-cyanoanilino)-4-nitropyridine** (0.445 g, 29%) separated: mp 222–224 °C (from methanol); ir (KBr) 3360, 2220, 1520, 1390 cm^{-1}; NMR (Me_2SO-d_6) δ 9.53 (s, 1 H, NH, exchangeable), 7.93 (d, 1 H, $J_{5,6}$ = 6 Hz, H_6), 7.30 (d, 2 H, $J_{o,m}$ = 9 Hz, H_o), 7.12 (d, 2 H, $J_{o,m}$ = 9 Hz, H_m), 7.01 (d, 1 H, $J_{3,5}$ = 2 Hz, H_5); mass spectrum *m/e* 240 ($M^{\cdot+}$, 15.5), 239 ($M^{\cdot+}$ − H, 100), 238 ($M^{\cdot+}$ − 2H, 95.5), 208 ($M^{\cdot+}$ − NO − 2H, 35.5), 193, 192, 166, 139, and 101.

Other 2-anilinopyridines obtained similarly are listed in Table II.

2-(*p*-Cyanoanilino)-4-ethoxypyridine. 2-(*p*-Cyanoanilino)-4-nitropyridine (0.360 g) was added to sodium ethoxide solution [from sodium (0.25 g) and ethanol (10 ml)]. The purple solution was stirred and heated under reflux for 3 h, diluted with boiling ethanol (70 ml), and filtered. The filtrate was evaporated and the residue was chromatographed on a column of silica gel. Elution with benzene gave **2-(*p*-cyanoanilino)-4-ethoxypyridine** (0.054 g, 15.1%): mp 138–139 °C (methanol); ir (KBr) 3340, 2220 cm^{-1}; mass spectrum *m/e* 239 ($M^{\cdot+}$, 72), 238 ($M^{\cdot+}$ − H, 69), 210 ($M^{\cdot+}$ − C_2H_5, 100).

Anal. Calcd for $C_{14}H_{13}N_3O$: C, 70.26; H, 5.49. Found: C, 70.17; H, 5.48.

Reaction of 4-Chloropyridine 1-Oxide with *p*-Nitrobenzenediazonium Tetrafluoroborate. A. 4-Chloro-2-(*p*-nitroanilino)pyridine. A solution of 4-chloropyridine 1-oxide (1.30 g) and *p*-nitrobenzenediazonium tetrafluoroborate (2.37 g) in acetonitrile (40 ml) was stirred at 0 °C for 1 h, then at room temperature overnight. The solvent was evaporated and the residue was crystallized from methanol (10 ml) to give an orange-yellow solid (2.076 g), mp 136–139 °C. Further recrystallization from methanol (20 ml) (charcoal) gave colorless crystals (1.226 g), mp 160–162 °C, which, after one more recrystallization from methanol, gave the analytically pure **4-methoxy-1-(4-nitrophenoxy)pyridinium tetrafluoroborate:** mp 152–153 °C; ir (KBr) 1510, 1345 (NO_2), 1110–1030 cm^{-1} (BF_4^-); NMR (CF_3CO_2H) δ 8.92 (d, 2 H, $J_{\alpha,\beta}$ = 7.5 Hz, H_α), 8.50 (d, 2 H, $J_{o,m}$ = 9.5 Hz, H_o), 7.77 (d, 2 H, $J_{\alpha,\beta}$ = 7.5 Hz, H_β), 7.24 (d, 2 H, $J_{o,m}$ = 9.5 Hz, H_m), and 4.37 (s, 3 H, OCH_3); mass spectrum *m/e* 294 ($M^{\cdot+}$ − 2HF, 50), 264 ($M^{\cdot+}$ − 2HF − NO, 40), 246 ($M^{\cdot+}$ − HBF_4, 100), 139 ($HOC_6H_4NO_2$, 45).

The mother liquor from the first recrystallization was evaporated and the residue was chromatographed on a column of silica gel (23 × 2.4 cm). Elution with $CHCl_3$ gave **4-chloro-2-(*p*-nitroanilino)pyridine** (0.175 g, 7%) (MeOH): mp 201–204 °C; ir (KBr) 3330, 1565, 1300 cm^{-1}; mass spectrum *m/e* 250 [$M^{\cdot+}$ (^{37}Cl) − 1, 7], 249 [$M^{\cdot+}$ (^{35}Cl), 10], 248 ($M^{\cdot+}$ − H, 22), 204 (55), 203 (10), 202 (14), 43 (100).

4-Chloro-2-(*p*-cyanoanilino)pyridine was obtained (15%) similarly from the reaction of *p*-cyanobenzenediazonium tetrafluoroborate and 4-chloropyridine 1-oxide in acetonitrile.

B. 4-Chloro-1-(4-nitrophenoxy)pyridinium Tetrafluoroborate. *A mixture of 4-chloropyridine 1-oxide (1.30 g) and p-nitrobenzenediazonium* tetrafluoroborate (2.37 g) in acetonitrile (30 ml) was stirred at room temperature overnight and then heated under reflux for 6 h. The solvent was evaporated in vacuo and the residue was triturated with benzene (20 ml) to give the 4-chloro salt (1.89 g, 56.2%) (from acetonitrile–ether, 1:3 v/v): mp 170 °C; ir (KBr) 1535, 1355, 1100–1030 cm^{-1}; NMR (CF_3CO_2H) δ 9.2 (d, 2 H, $J_{\alpha,\beta}$ = 6.5 Hz, H_α), 8.45 (m, 4 H, H_β and H_o), 7.34 (d, 2 H, $J_{o,m}$ = 9 Hz, H_m); mass spectrum *m/e* 300 [$M^{\cdot+}$ (^{37}Cl) − 2HF, 15], 298 [$M^{\cdot+}$ (^{35}Cl) − 2HF, 45], 270 (13), 268 (39), 252 (25), 250 (75), 206 (15), 204 (45), 139 ($HOC_6H_4NO_2^{\cdot+}$, 100). Recrystallization from methanol gave 4-methoxy-1-(4-nitrophenoxy)pyridinium tetrafluoroborate, mp 151.5–153 °C, identical with the sample obtained above.

Base-Catalyzed Rearrangement of Aryloxypyridinium Salts. The general procedure used will be illustrated by means of two examples. The products formed and analytical data for new compounds are given in Table III.

2-(2-Hydroxy-5-nitrophenyl)pyridine. A solution of 1-(4-nitrophenoxy)pyridinium tetrafluoroborate (1.52 g, 0.005 mol) and potassium phenoxide (0.79 g, 0.006 mol) in acetonitrile (20 ml) was heated under reflux for 1 h. The solvent was evaporated and the residue was treated with 2 *N* HCL (20 ml). Extraction with ether (3 × 30 ml) and evaporation of the dried ($MgSO_4$) extract gave the phenol (0.703 g, 65%): mp 216–217 °C (ethanol); ir (KBr) 2600 (−N^+H=), 1480, 1330 cm^{-1} (NO_2); λ_{max} (CH_3CN) 248, 287, 315 nm; NMR (CF_3CO_2H) δ 8.93–8.67 (m, 5 H), 8.00 (t, 1 H, *J* = 7 Hz), 7.37 (d, 1 H, *J* = 10 Hz); mass spectrum *m/e* 216 ($M^{\cdot+}$, 100), 200 ($M^{\cdot+}$ − O), 186 ($M^{\cdot+}$ − NO), 170 ($M^{\cdot+}$ − NO_2), 142 ($M^{\cdot+}$ − NO_2 − CO).

2-(2-Hydroxy-5-nitrophenyl)-4-methylpyridine. Triethylamine (0.46 g, 0.0045 mol) was added to a solution of 4-methyl-1-(4-nitrophenoxy)pyridinium tetrafluoroborate (0.954 g, 0.003 mol) in acetonitrile (20 ml) and the solution was heated under reflux for 1 h. The solvent was evaporated, the residue was extracted with hot ether (4 × 40 ml), the ether extract was evaporated, and the residue was chromatographed on a column of silica gel. Elution with benzene (300 ml) gave *p*-nitrophenol (0.207 g, 49.7%), mp 113–114 °C. Elution with benzene–chloroform (80:20 v/v, 400 ml) gave **2-(2-hydroxy-5-nitrophenyl)-4-methylpyridine** (66 mg, 9.6%): mp 204–205.5 °C (EtOH); ir (KBr) 2600 cm^{-1}; NMR ($CDCl_3$ + 3 drops of CF_3CO_2H) δ 8.9–8.6 (m, 2 H, H_α and H_6), 8.5–8.2 (m, 2 H, H_β and H_4), 7.85 (dd, $J_{\alpha\beta}$ = 5.5, $J_{\beta\beta'}$ = 1.2 Hz, $H_{\beta'}$), 7.30 (d, 1 H, $J_{3,4}$ = 9 Hz, H_3), 2.62 (s, 3 H, CH_3); mass spectrum *m/e* 230 ($M^{\cdot+}$, 100), 214 (15), 200 (20), 184 (28).

Authentic 2-(2-Hydroxy-5-nitrophenyl)pyridine. 2-(2-Methoxy-5-nitrophenyl)pyridine[9] (0.83 g) was heated in hydrobromic acid (48%, 16 ml) for 7 h. The mixture was adjusted to pH 3 and extracted with ether to give the phenol (0.146 g, 13%): mp 213–214° (EtOH), identical in all respects with the sample obtained above.

2-(2-Hydroxy-4-nitrophenyl)pyridine (7). 2-(2-Methoxy-4-nitrophenyl)pyridine (0.41 g) [obtained in low (6%) yield from Gomberg–Hey arylation of pyridine with 2-methoxy-4-nitroben-

zenediazonium chloride followed by chromatography on silica gel and elution with chloroform] was heated with 48% HBr as above, and the mixture adjusted to pH 8 and extracted with chloroform to give 7 (0.33 g, 85%), mp 186–187 °C (MeOH), identical with the sample obtained by base-catalyzed rearrangement of 1-(3-nitrophenoxy)pyridinium tetrafluoroborate.

The nitro compound was reduced with sodium polysulfide[16] in methanol to give 2-(4-amino-2-hydroxyphenyl)pyridine (**9**, 16%): mp 107–108 °C (benzene); ir (KBr) 3450, 3360, 2500 cm^{-1}; NMR (Me_2SO-d_6) δ 8.84 (d, 1 H, $J_{5,6}$ = 5 Hz, H_6), 8.28 (t, 2 H, $J_{3,4} = J_{4,5}$ = 5 Hz, H_3, H_4), 8.07 (d, 1 H, $J_{\beta\gamma}$ = 9 Hz, H_γ), 7.58 (dt, 1 H, $J_{5,6} = J_{4,5}$ = 5, $J_{3,5}$ = 2 Hz, H_5), 6.66 (dd, $J_{\beta\gamma}$ = 9, $J_{\alpha\beta}$ = 2 Hz, H_β), 6.57 (d, 1 H, $J_{\alpha\beta}$ = 2 Hz, H_α), 5.99 (s, 2 H, exchangeable with D_2O, NH_2); mass spectrum *m/e* 186 ($M^{\cdot+}$, 100), 185 (40.5), 79 (26.5).

Hydrolysis of 1,1′-Di(2,4-dinitrophenoxy)-4,4′-dipyridylium Ditetrafluoroborate (21). A. A suspension of the salt (1.74 g) in water (40 ml) was boiled under reflux for 15 min and then concentrated down to 10 ml. A yellow precipitate separated on cooling and was extracted with hot chloroform (50 ml). Evaporation of the extract gave 2,4-dinitrophenol (0.68 g, 74%): mp 111 °C, identical with an authentic sample. The chloroform-insoluble portion was recrystallized from water to give **4,4′-di(2-pyridone) (22,** 0.34 g, 72%): mp >300 °C; ir (KBr) 3250–2600 (bonded NH), 1700–1600 cm^{-1} (bonded C=O); NMR (CF_3CO_2H) δ 8.33 (d, 2 H, $J_{5,6}$ = 6 Hz, H_6), 7.6 (m, 6 H, H_3, H_5, and NH); mass spectrum *m/e* 188 ($M^{\cdot+}$, 100), 187 (30), 160 (10), 159 (16), 132 ($M^{\cdot+}$ − 2CO, 22), 104 (20).

Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.83; H, 4.26; N, 14.89. Found: C, 63.64; H, 4.30; N, 14.86.

B. The salt (3.78 g) and triethylamine (0.61 g) in nitromethane (150 ml) were heated under reflux for 2 h. The only product isolated from the oil obtained was 2,4-dinitrophenol (0.58 g, 31.5%), mp 111–112 °C.

2-(3-Bromo-5-cyano-2-hydroxyphenyl)pyridine. Bromine (0.75 g) in acetic acid (6 ml) was added at room temperature with stirring to 2-(5-cyano-2-hydroxyphenyl)pyridine (0.39 g) in acetic acid (6 ml). The stirred solution was heated at 100 °C for 3 h, the solvent was evaporated, and the residue was recrystallized from methanol to give the bromo compound (0.39 g, 72%): mp 175–178°; ir (KBr) 2220 cm^{-1}; NMR (CF_3CO_2H) δ 8.87 (dd, 1 H, $J_{5,6} = J_{4,6}$ = 2 Hz, H_6), 8.71 (dt, 1 H, $J_{4,6}$ = 2, $J_{4,5} = J_{3,4}$ = 8 Hz, H_4), 8.37 (d, 1 H, $J_{3,4}$ = 8 Hz, H_3), 8.16 (s, 2 H, H_o and H_p), 8.08 (dd, 1 H, $J_{4,5}$ = 8, $J_{5,6}$ = 6 Hz, H_5); mass spectrum *m/e* 276 (93), 274 (100).

Anal. Calcd for $C_{12}H_7BrN_2O$: C, 52.39; H, 2.57. Found: C, 52.42; H, 2.66.

A similar bromination of 2-(2-hydroxy-3-nitrophenyl)pyridine afforded **2-(5-bromo-2-hydroxy-3-nitrophenyl)pyridine** (17%), mp 163–164 °C (MeOH).

Anal. Calcd for $C_{11}H_7BrN_2O_3$: C, 44.76, H, 2.40. Found: C, 44.95; H, 2.45.

Reaction of 1-Aminopyridinium Tetrafluoroborates with Aryldiazonium Tetrafluoroborates in Nitrile Solvents. This will be illustrated by means of a few typical examples. The properties of compounds so prepared are given in Tables IV–VI.

1-[(*N*-*p*-Cyanophenylacetimidoyl)amino]pyridinium Tetrafluoroborate. A solution of 1-aminopyridinium tetrafluoroborate (0.91 g) and *p*-cyanobenzenediazonium tetrafluoroborate (1.09 g) in acetonitrile (25 ml) was stirred at room temperature for 6 h and then boiled under reflux for 1.5 h. The brown tarry residue left on evaporation of the solvent was recrystallized from methanol to give the acetimidoylamino salt (0.88 g, 54%): mp 282–283 °C; ir (KBr) 3360, 3240 (NH), 2220 (CN), 1620 (C=N), 1140–1000 cm^{-1} (BF_4^-); NMR (Me_2SO-d_6) δ 10.82 (s, 1 H, NH), 9.48 (d, 2 H, $J_{\alpha,\beta}$ = 6 Hz, H_α), 9.03 (t, 1 H, $J_{\beta,\gamma}$ = 7 Hz, H_γ), 8.68 (m, 2 H, H_β), 8.38 (t, 4 H, phenyl hydrogens), 2.73 (s, 3 H, CH_3); mass spectrum *m/e* 236 ($M^{\cdot+}$ − HBF_4, 24), 235 ($M^{\cdot+}$ − H − HBF_4, 100), 195 (9), 79 (77), 52 (62), 49 (95).

1-[(*N*-*p*-Nitrophenylcyanoacetimidoyl)amino]pyridinium Tetrafluoborate (15, R^2 = $CNCH_2$; X = 4-NO_2; R^1 = H). A solution of 1-aminopyridinium tetrafluoroborate (0.546 g) and *p*-nitrobenzenediazonium tetrafluoroborate (0.771 g) in malononitrile (5 g) was stirred for 6 h at 90 °C. The mixture was chromatographed on a column of silica gel (40 g). Elution with chloroform (1000 ml) gave malononitrile. Further elution with $CHCl_3$ gave ω-cyano-*p*-nitroacetanilide (55 mg, 9%): mp 221–222 °C (lit.[17] mp 198–202 °C); ir (KBr) 3290, 2270, 1710, 1620, 1560, 1330 cm^{-1}; mass spectrum *m/e* 206 ($M^{\cdot+}$ + 1, 13), 205 ($M^{\cdot+}$, 100), 165 ($M^{\cdot+}$ − CH_2CN, 25), 159 ($M^{\cdot+}$ − NO_2, 5), 138 ($NO_2C_6H_4NH_2^+$, 55), 108 (71), 92 (41). Further elution with $CHCl_3$–MeOH gave **1-[(*N*-*p*-nitrophenylcyanoacetimidoyl)amino]pyridinium tetrafluoroborate** (0.636 g, 57%): mp 187–188 °C (MeOH); ir (KBr) 3320, 2260, 1635, 1620, 1550, 1335, 1100–1000 cm^{-1}; NMR (Me_2SO-d_6) δ 10.90 (s, 1 H, NH), 9.10 (d, 2 H, $J_{\alpha,\beta}$ = 6 Hz, H_α), 8.61 (t, 1 H, $J_{\beta,\gamma}$ = 6.8 Hz, H_γ), 8.33 (d, 2 H, $J_{o,m}$ = 9 Hz, H_o), 8.25 (dd, 2 H, $J_{\alpha,\beta}$ = 6 Hz, H_β), 7.98 (d, 2 H, $J_{o,m}$ = 9 Hz, H_m), 4.00 (s, 2 H, CH_2); mass spectrum *m/e* 280 ($M^{\cdot+}$ − H − HBF_4, 6), 279 (50), 249 (16), 79 (93), 52 (64), 49 (100).

1-(*N*-Butyrimidoylamino)iminopyridinium Tetrafluoroborate (16, R = $CH_3CH_2CH_2$; R^1 = H). A solution of 1-aminopyridinium tetrafluoroborate (0.91 g) and *p*-trifluoromethylbenzenediazonium tetrafluoroborate (1.35 g) in butyronitrile (20 ml) was stirred and boiled under reflux for 2 h. The solvent was evaporated in vacuo and the residue was chromatographed on a column of silica gel. Elution with chloroform–ethanol (10:1 v/v) gave **1-(*N*-butyrimidoylamino)iminopyridinium tetrafluoroborate** (0.34 g, 28%): mp 159–160 °C (MeOH); ir (KBr) 3440, 3370, 3280, 1660, 1640, 1170–1000 cm^{-1}, NMR (Me_2SO-d_6) δ 8.75 (dd, 2 H, $J_{\alpha,\beta}$ = 4/5= $J_{\alpha,\gamma}$ = 1.5 Hz, H_α), 8.45 (m, 1 H, H_γ), 8.08 (dd, 2 H, $J_{\alpha,\beta}$ = 4.5, $J_{\beta,\gamma}$ = 7.5 Hz, H_β), 7.3 (br s, 2 H, D_2O exchange, NH_2), 2.31 (t, 2 H, *J* = 7.5 Hz, $CH_2CH_2CH_3$), 1.58 (sextuplet, 2 H, *J* = 7.5 Hz, $CH_2CH_2CH_3$), 1.01 (t, 3 H, *J* = 7.5 Hz, CH_3); mass spectrum *m/e* 164 ($M^{\cdot+}$, 19), 133 ($M^{\cdot+}$ − CH_3 − NH_2, 25), 121 ($M^{\cdot+}$ − C_3H_7, 100), 79 (C_5H_5N, 68).

1-[(*N*-*p*-Cyanophenylacetimidoyl)imino]pyridinium Ylide (19, R = H; X = *p*-CN). 1-[(*N*-*p*-Cyanophenylacetimidoyl)amino]pyridinium tetrafluoroborate (1.30 g) and sodium methoxide (0.54 g) in acetonitrile (30 ml) were heated for 3 h. The solvent was evaporated to dryness and the residue was extracted with boiling benzene (600 ml). The extracts were evaporated to give the ylide (0.633 g, 67%): mp 159–160 °C (from ethyl acetate); ir (KBr) 2220 cm^{-1}; NMR (Me_2SO-d_6) δ 9.12 (d, 2 H, $J_{\alpha,\beta}$ = 6 Hz, H_α), 8.39 (t, 1 H, $J_{\beta,\gamma}$ = 7 Hz, H_γ), 8.13 (br t, 2 H, *J* = 7 Hz, H_β), 7.8 (d, 2H, $J_{o,m}$ = 8 Hz, H_o), 7.04 (d, 2 H, $J_{o,m}$ = 8 Hz, H_m), 2.24 (s, 3 H, CH_3); mass spectrum *m/e* 236 ($M^{\cdot+}$, 16), 235 ($M^{\cdot+}$ − H, 59), 194 (9), 121 (17), 118 (17), 102 (20), 81 (33), 79 (100).

Treatment of the ylide with a solution of tetrafluoroboric acid regenerated the starting salt.

Treatment of the ylide with acetyl chloride in benzene gave **1-[(*N*-*p*-cyanophenylacetimidoyl)amino]pyridinium chloride** (56%); mp 304–305 °C (methanol–ethyl acetate); ir (KBr) 3280, 2220, 1640 cm^{-1}; NMR (D_2O) δ 8.78 (d, 2 H, $J_{\alpha,\beta}$ = 6 Hz, H_α), 8.60 (t, 1 H, $J_{\beta,\gamma}$ = 7.5 Hz, H_γ), 8.18 (dd, 2 H, $J_{\alpha,\beta}$ = 6, $J_{\beta,\gamma}$ = 7.5 Hz, H_β), 7.88 (s, 4 H, phenyl hydrogens), 2.13 (s, 3 H, CH_3); mass spectrum *m/e* 236 ($M^{\cdot+}$ − Cl, 26), 235 ($M^{\cdot+}$ − HCl, 100), 188 ($CNC_6H_4NH_2^{\cdot+}$, 43).

Anal. Calcd for $C_{14}H_{13}ClN_4$: C, 60.53; H, 4.72. Found: C, 60.64; H, 4.77.

Attempted Rearrangement of Ylide 19 (R = H; X = *p*-CN) with Sodium Hydride. A mixture of the ylide (128 mg) and sodium hydride (26 mg) in acetonitrile (20 ml) was stirred overnight at room temperature and then heated under reflux for 12 h. Water (5 ml) was added. Workup of the mixture gave starting ylide (104 mg, 81%).

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Registry No.—**1** (R^2 = 4-NO_2; R^3 = H), 456-27-9; **1** (R^2 = 4-CN; R^3 = H), 2252-32-6; **1** (R^2 = 4-CF_3; R^3 = H), 36407-40-6; **1** (R^2 = 3-NO_2; R^3 = H), 586-36-7; **1** (R^2 = 2-NO_2; R^3 = H), 365-33-3; **1** (R^2 = 2-CF_3; R^3 = H), 447-59-6; **1** (R^2 = 2-CN; R^3 = H), 55165-45-2; **1** (R^2 = 2-NO_2; R^3 = 4-NO_2), 345-12-0; **1** (R^2 = 3-NO_2; R^3 = 5-NO_2), 369-20-0; **1** (R^2 = 3-Cl; R^3 = H), 456-39-3; **1** (R^2 = R^3 = H), 369-57-3; **1** (R^2 = 4-Cl; R^3 = H), 673-41-6; **2** (R^1 = H), 694-59-7; **2** (R^1 = 4-CH_3), 1003-67-4; **2** (R^1 = 4-C_6H_4), 1131-61-9; **2** (R^1 = 4-OCH_3), 22346-75-4; **2** (R^1 = 4-OC_6H_5), 33399-53-0; **2** (R^1 = 4-Cl), 1121-76-2; **2** (R^1 = 4-CN), 14906-59-3; **2** (R^1 = 2-OCH_3), 10242-36-1; **2** [R^1 = 4-(4-pyridyl 1-oxide], 24573-15-7; **2** (R^1 = 4-NO_2), 1124-33-0; **8**, 58425-96-0; **9**, 58425-97-1; **10** (R = 4-CN), 58673-26-0; **10** (R = 2-CH_3), 58425-99-3; **10** (R = 3,5-Me_2), 58426-01-0; **10** (R = 2,6-Me_2), 58426-02-1; **22**, 58426-03-2; 2-(3-bromo-5-cyano-2-hydroxyphenyl)pyridine, 58426-04-3; 2-(5-bromo-2-hydroxy-3-nitrophenyl)pyridine, 58448-77-4; 1-[(*N*-*p*-cyanophenylacetimidoyl)amino]pyridinium chloride, 58426-05-4; 2-(*p*-cyanoanilino)-4-ethoxypyridine, 58426-06-5.

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Mesoionic Compounds. 38. The *anhydro*-2-Aryl-1,3-dithiolium Hydroxide System[1]

Kevin T. Potts, Dilip R. Choudhury, Arthur J. Elliott, and Udai P. Singh*

Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12181

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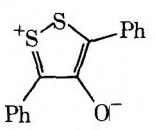
anhydro-4-Hydroxy-2-phenyl-1,3-dithiolium hydroxide has been prepared from thiobenzoylthioglycollic acid, acetic anhydride, and triethylamine at 0–10 °C and the product previously assigned this structure shown to be *anhydro*-4-hydroxy-2-phenyl-5-(thiobenzoylthiomethylcarbonyl)-1,3-dithiolium hydroxide. This mesoionic ring system undergoes ready cycloaddition of acetylenic dipolarophiles yielding substituted thiophenes with elimination of carbonyl sulfide. With olefinic dipolarophiles and azirines stable 1:1 adducts were formed.

Interest in the chemistry of five-membered ring systems containing sulfur has increased considerably over the past several years, particular attention being paid to those systems containing two sulfur atoms in the 1,2 positions[2] and in the 1,3 positions.[3] Cycloaddition reactions have played a prominent part in these studies,[4] and have resulted in several useful synthetic procedures. Mesoionic derivatives[5] of both the 1,2-dithiole and 1,3-dithiole ring systems can be devised and a study of their synthesis and properties was initiated as part of our interests in this area.

anhydro-3,5-Diphenyl-4-hydroxy-1,2-dithiolium hydroxide (1) has been synthesized[6] from 1,1,3,3-tetrabromo-1,3-diphenylacetone and potassium ethyl xanthate, or from 1,3-diphenylpropanetrione and H_2S–HCl, followed by Et_3N.[7] We have found this ring system to be completely unresponsive to a variety of dipolarophiles[8] whereas *anhydro*-4-hydroxy-2-phenyl-1,3-dithiolium hydroxide (**2**, R = Ph; R^1 = H) was an extremely reactive system whose reactions are described below.



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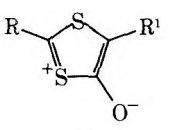


2

3

The ring system **2** was described as being prepared from thiobenzoylthioglycollic acid (**3**, R = Ph; R^1 = H) and acetic anhydride–boron trifluoride.[9a] The corresponding exocyclic imino derivatives have also been prepared by cyclization of cyanomethyl dithiobenzoate with anhydrous HCl or acid chlorides,[9b] and an unstable ortho-protonated derivative of **2** (R = Ph; R^1 = H) was obtained by cyclization of carboxymethyl dithiobenzoate with perchloric acid,[9c] a convenient cyclization agent for the preparation of a variety of 1,3-dithioles.[3]

Repetition of the reported procedure[9a] gave a deep-red, crystalline product, mp 185–186 °C dec, as described previously when a reaction time of several minutes was used. Longer reaction times resulted in considerable polymer formation. This red product failed to undergo cycloadditions with several dipolarophiles and, on examination of its spectral characteristics, they were found to be incompatible with the assigned structure. The mass spectrum showed an ion at *m/e* 388 (5%), most likely a molecular ion which, in conjunction with analytical data, established the molecular formula as $C_{18}H_{12}O_2S_4$. The NMR data for this product indicated the presence of two phenyl groups [δ 7.48 (m, 10)] and two methylene protons which appeared as two AB doublets (J = 16.5 Hz) at δ 4.33–4.08 and 4.01–3.75, and the infrared spectrum showed two absorptions at 1690 and 1590 cm^{-1}, conceivably due to two carbonyl groups related to each other in such a way that an exocyclic negative charge was delocalized over both groups. These data are most satisfactorily accommodated by the structure *anhydro*-4-hydroxy-2-phenyl-5-(thiobenzoylthiomethylcarbonyl)-1,3-dithiolium hydroxide (**2**, R = Ph; R^1 = $COCH_2SCSPh$).

This "overacylation" of a mesoionic system under similar cyclodehydration conditions has been observed in the oxazole,[10] imidazole,[11] and thiazole[12] ring systems, and the spectral parameters of this present product are consistent with those of the comparable products in these ring systems. Indicative of a high degree of charge density at that position of the nucleus, it also indicates considerable potential in 1,3-dipolar cycloaddition reactions. However, these acylated products themselves often do not undergo cycloadditions owing to delocalization of the negative charge of the masked 1,3-dipole over the carbonyl groups.

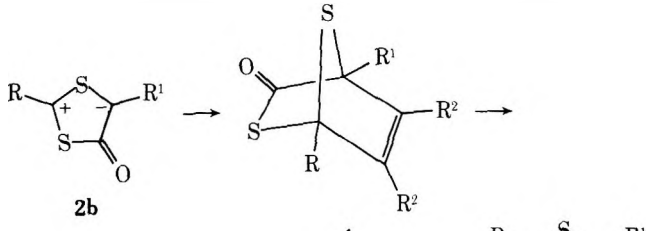
The acylation can often be avoided by the use of Et_3N and low reaction temperatures.[12c] When the thiobenzoylthioglycollic acid (**3**, R = Ph; R^1 = H) was treated with a mixture of Et_3N–Ac_2O (1:3) at 0–10 °C for several minutes only, glistening scarlet needles, mp 113–115 °C dec, were obtained. That this product was the desired mesoionic system, *anhydro*-4-hydroxy-2-phenyl-1,3-dithiolium hydroxide (**2**, R = Ph; R^1 = H) was evident from the following considerations. Analytical and mass spectral data [$M^{\cdot+}$ 194 (40%)] showed the molecular formula to be $C_9H_6S_2O$ and, in addition to aromatic protons at δ 7.51 (5), the NMR spectrum showed only a sharp

singlet at δ 6.06. This chemical shift, together with a ν_{CO} at 1610 cm^{-1}, is characteristic of mesoionic systems,[12c] and the correctness of this structural assignment was evident from the chemical transformations described below. The chemical shift δ 6.06 for the C_5 H should be compared with those of analogous protons in 1,3-dithiolium salts.[9c] In these salts the C_5 H usually falls in the range δ 8.73–4.92, depending on the 2 substituent, and the shift to a high field in this present system no doubt reflects the increased shielding at the C-5 position caused by delocalization of the exocyclic negative charge.

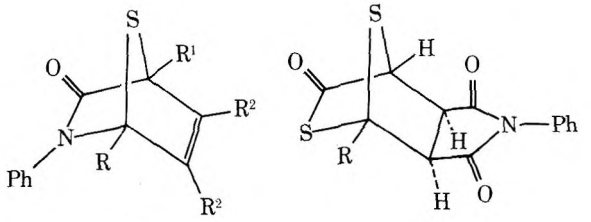
Use of *p*-chlorothiobenzoylthioglycollic acid (**3**, R = *p*-ClC_6H_4; R^1 = H) and *p*-methoxythiobenzoylthioglycollic acid (**3**, R = *p*-$CH_3OC_6H_4$; R^1 = H) in the above reaction gave the corresponding 2-*p*-chlorophenyl and 2-*p*-methoxyphenyl derivatives of **2**. These mesoionic compounds were moderately sensitive in solution to traces of moisture, undergoing hydrolysis to their precursors, and optimum results were obtained only by using very pure dithioglycollic acids and working under "drybox" conditions with anhydrous solvents. They are quite stable in the dry, solid state.

5-Phenyl and 5-methyl derivatives of **2** have also been prepared[13] by Ac_2O–Et_3N cyclization of the corresponding disubstituted thioglycollic acid. However, the additional substituent renders the reaction conditions far less critical than those employed for the synthesis of **2** (R = aryl; R^1 = H), a feature which has also been observed in the *anhydro*-4-hydroxy-2-phenylthiazolium hydroxide system.[14]

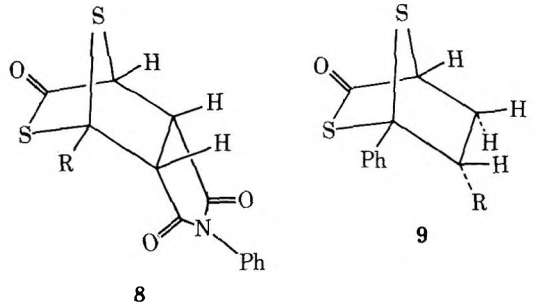
The ring system **2** contains a masked 1,3-dipole of the thiocarbonyl ylide type represented by **2b**. Dimethyl acetylenedicarboxylate added readily to **2** (R = Ph; R^1 = H) giving dimethyl 2-phenylthiophene-3,4-dicarboxylate (**5**, R = Ph; R^1 = H; R^2 = $COOCH_3$) in reasonable yield. The 2,7-dithiabicyclo[2.2.1]heptane **4** (R = Ph; R^1 = H; R^2 = $COOCH_3$) was the likely intermediate in the cycloaddition but elimination of carbonyl sulfide occurred so readily at 80 °C



2b **4** **5**



6 **7**



8 **9**

that **4** could not be isolated. Similar facile eliminations of carbonyl sulfide have been observed from the initial cycloadducts from *anhydro*-5-hydroxy-3-methyl-2-phenylthiazolium hydroxide and acetylenic dipolarophiles.[12c] The 2-*p*-methoxyphenyl- and 2-*p*-chlorophenylthiophenes **5** (R = *p*-$CH_3OC_6H_4$ and *p*-ClC_6H_4; R^1 = H; R^2 = $COOCH_3$) were obtained readily from the corresponding substituted derivatives of **2** (R = *p*-$CH_3OC_6H_4$ and *p*-ClC_6H_4; R^1 = H). Similarly dibenzoylacetylene and **2** (R = Ph; R^1 = H) gave[15] the corresponding thiophene **5** (R = Ph; R^1 = H; R^2 = COPh). The structures of these thiophenes were readily established by analytical and spectral data (Experimental Section). Thus in **5** (R = Ph; R^1 = H; R^2 = $COOCH_3$) the NMR spectrum showed a singlet proton at δ 7.98, consistent with the 5 proton being deshielded by the 4-$COOCH_3$ substituent and shifted downfield from the usual chemical shift of δ 7.19 in thiophene.[16] The mass spectra of the thiophenes all showed molecular ions and fragmentation patterns consistent with the assigned structures.

It has also been shown[17] that the corresponding 5-aryl and 5-methyl derivatives of **2** (R = R^1 = aryl; R = aryl, R^1 = CH_3) undergo ready cycloaddition with similar acetylenic dipolarophiles yielding the appropriate thiophenes **5** (R = R^1 = aryl; R = aryl, R^1 = CH_3). Thus in conjunction with the *anhydro*-2,3,5-triaryl-4-hydroxythiazolium hydroxides,[14] the ring system **2** is a useful synthon for a variety of thiophenes not readily available by other routes.

N-Phenylmaleimide underwent ready reaction with **2** (R = Ph; R^1 = H) in refluxing benzene over 6 h. The product was shown to be a simple 1:1 cycloadduct of molecular formula $C_{19}H_{13}NO_3S_2$ from analytical and spectral data, the latter also allowing a choice between the exo adduct **7** (R = Ph) and the endo adduct **8** (R = Ph). A one-proton doublet of doublets (*J* = 6.6, 1.0 Hz) at δ 3.93 (H_5), a doublet (*J* = 6.6 Hz) at δ 4.29 (H_6), and a doublet at δ 4.88 (*J* = 1.0 Hz) are only compatible with the endo adduct **8** (R = Ph), these chemical shifts and coupling constants also being consistent with those observed in related adducts.[18–20] Similar endo adducts **8** (R = *p*-$CH_3OC_6H_4$, *p*-ClC_6H_4) were obtained from **2** (R = *p*-$CH_3OC_6H_4$, *p*-ClC_6H_4; R^1 = H) and *N*-phenylmaleimide, and their chemical shifts and coupling constants are described in the Experimental Section. The cycloadducts **8** did not show molecular ions in their mass spectra, an ion corresponding to (M – COS) being observed together with those resulting from further fragmentation of the system. In contrast the reaction of **2** (R = R^1 = Ph) and *N*-phenylmaleimide required xylene at 150 °C and in this case a mixture of the exo and endo adducts was obtained.[18]

Acrylonitrile and ethyl acrylate also give 1:1 adducts with **2** (R = Ph; R^1 = H). The adduct from the former was assigned structure **9** (R = CN) on the basis of coupling of the bridgehead proton (H_4) to two other protons, indicating that the cyano group is in the 6 position. The chemical shifts and coupling constants for $H_{5\alpha}$, $H_{5\beta}$, and $H_{6\alpha}$ (Experimental Section) show that the cyano group is in an endo configuration. Although the NMR spectrum of the ethyl acrylate adduct was similar in gross features to that of the acrylonitrile product suggesting an endo configuration for the ethoxycarbonyl group, the overlapping of the chemical shifts made it difficult to assign the configuration of this group with any degree of certainty.

The mesoionic system **2** (R = Ph; R^1 = H) failed to yield an isolable product with diphenylcyclopropenone and 3-methyl-2-phenylazirine owing to its decomposition in refluxing toluene over extended reaction periods. However its 2,5-diphenyl derivative is considerably more stable both thermally and to traces of moisture and has been reported[21] to give 2,3,5,6-tetraphenyl-4*H*-thiopyran-4-thione with diphenylcyclopropenethione. We have found that **2** (R = R^1 =

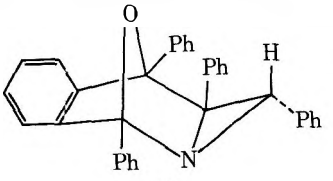
Ph) also reacts with azirines and in refluxing xylene with 2,3-diphenyl-1-azirine gave a multicomponent reaction mixture. The major product, isolated by chromatography (silica gel), was shown by its analytical and spectral data to be a 1:1 adduct. Earlier studies with 1-azirines in cycloadditions[22] suggest an addition of the "masked" ylide in **2** to the C=N of the azirine, with the possibility of some subsequent, skeletal rearrangement.

This thermally stable product (ν_{CO} 1690 cm^{-1}) had retained the skeletal arrangement of atoms present in the substrate **2** and its structure has been assigned in analogy with the structures of the products obtained[23] from 1,3-diphenylisobenzofuran and azirines and on the basis of the following spectral data and chemical reactions. Its NMR spectrum showed a singlet at δ 5.66 and a complex aromatic multiplet at δ 8.18–6.76. A second, minor isomeric product isolated from this reaction showed a singlet proton at δ 5.95 in addition to the aromatic multiplet. In the adduct **10**, the aziridine ring proton was observed at δ 4.52, being deshielded by the oxido bridge. This deshielding was helpful in establishing the structures of the adducts obtained above. Thus the major adduct was assigned structure **11** (R = Ph) with an endo aziridine proton (deshielding $\approx$ 2.14 ppm) and the minor adduct was assigned structure **12** (R = Ph) with an exo aziridine proton (deshielding $\approx$ 2.43 ppm). Oxidation of **11** (R = Ph) with 1 equiv of *m*-chloroperbenzoic acid in methylene chloride gave the corresponding sulfoxide **13** (R = Ph) (ν_{SO} 1077 cm^{-1}) whose aziridine proton had undergone only a small downfield shift (0.1 ppm) which would be anticipated for a proton in this configuration.

Two minor products were isolated in insufficient amounts for complete characterization from the initial cycloaddition and were thought to be 2,4,5-triphenylthiazole and 2,4,5-triphenyl-6*H*-1,3-thiazin-6-one on the basis of mass spectral fragmentation patterns.

3-Methyl-2-phenylazirine reacted with **2** (R = R^1 = Ph) in refluxing xylene over 11 h. The product isolated after chromatography (57%) was likewise identified as a 1:1 adduct (ν_{CO} 1680 cm^{-1}). Two quartets at δ 4.45 and 3.71 and two doublets at δ 1.35 and 1.11 demonstrated the presence of the two isomers **12** (R = CH_3) and **11** (R = CH_3), respectively in the ratio of 1:2.25. Attempts to separate this mixture by chromatography were unsuccessful.

Oxidation of this mixture with *m*-chloroperbenzoic acid in CH_2Cl_2 at room temperature resulted in the isolation of only one sulfoxide (ν_{SO} 1090 cm^{-1}) with a quartet at δ 5.48 and a doublet at δ 1.18. This downfield shift in the methine resonance (1.03 ppm) indicates that the isolated sulfoxide has structure **14** (R = CH_3), implying a syn relationship between the S–O group and the aziridine proton and hence derived from **12** (R = CH_3).



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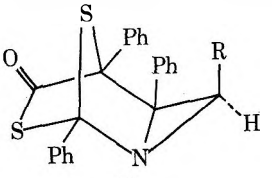

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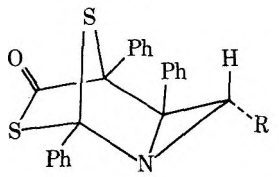

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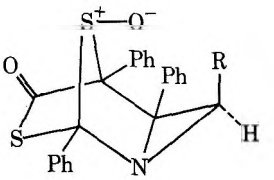

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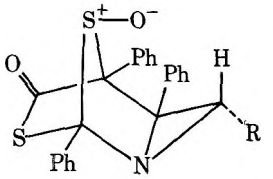

14

It is interesting that exo adducts only were isolated from azirines and the mesoionic system **2** whereas with olefinic dipolarophiles endo adducts were obtained. As in the adducts derived from 1,3-diphenylisobenzofuran,[23] this may be explained in terms of an unfavorable increase in energy for the endo transition state as a result of secondary orbital interactions. Although it was not possible to detect it experimentally, the initial formation of the endo adduct with a subsequent retro-1,3-dipolar reaction with the ultimate formation of the exo adduct cannot be excluded.

Experimental Section[24]

***anhydro*-4-Hydroxy-2-phenyl-1,3-dithiolium Hydroxide (2, R = Ph; R^1 = H).** Thiobenzoylthioglycollic acid[25] (2.5 g, 0.012 mol) was dissolved in a mixture of acetic anhydride (2 ml) and triethylamine (5 ml) at room temperature and the reaction mixture was cooled at 0 °C for 10 min, crystallization being induced by scratching the walls of the reaction vessel. Addition of anhydrous ether caused additional product to separate and this was collected and washed with anhydrous ether using "drybox" conditions throughout. The product of analytical purity was obtained as glistening scarlet needles: 1.75 g (77%); mp 113–115 °C dec; ir (KBr) 1610 cm^{-1} (CO); λ_{max} (anhydrous CH_3OH) 220 nm (log ϵ 4.24), 265 (3.96), 285 (3.89), and 325 (3.46); NMR ($CDCl_3$) δ 6.06 (s, 1, H_4), 7.51 (m, 5, aromatic); $M^{\cdot+}$ 194 (40).

Anal. Calcd for $C_9H_6OS_2$: C, 55.67; H, 3.12. Found: C, 55.55; H, 3.40.

Attempted recrystallization of the product always resulted in some ring opening occurring owing to traces of moisture present in the solvent.

Similarly *anhydro*-4-hydroxy-2-*p*-methoxyphenyl-1,3-dithiolium hydroxide (**2**, R = *p*-$CH_3OC_6H_4$; R^1 = H) was obtained from *p*-methoxythiobenzoylthioglycollic acid (**3**, R = *p*-$CH_3OC_6H_4$; R^1 = H) as brilliant, scarlet-red needles: 80%; mp 143–145 °C dec; ir (KBr) 1600 cm^{-1} (CO); λ_{max} (anhydrous CH_3OH) 230 nm (log ϵ 4.21), 255 (3.83), and 330 (3.83); NMR ($CDCl_3$) δ 3.88 (s, 3, OCH_3), 5.90 (s, 1, H_4), 6.88–7.03 (AB d, 2, J = 9.0 Hz, aromatic), 7.51–7.66 (AB d, 2, J = 9.0 Hz, aromatic); $M^{\cdot+}$ 224 (52).

Anal. Calcd for $C_{10}H_8O_2S_2$: C, 53.58; H, 3.60. Found: C, 53.80; H, 3.65.

anhydro-4-Hydroxy-2-*p*-chlorophenyl-1,3-dithiolium hydroxide (**2**, R = *p*-ClC_6H_4; R′ = H) also formed red needles, 75%, mp 160 °C dec.

Anal. Calcd for $C_9H_5ClOS_2$: C, 47.20; H, 2.19. Found: C, 47.11; H, 2.14.

***anhydro*-4-Hydroxy-2-phenyl-5-(thiobenzoylthiomethylcarbonyl)-1,3-dithiolium Hydroxide (2, R = Ph; R^1 = $COCH_2SCSPh$).** Thiobenzoylthioglycollic acid (4.25 g), dissolved in acetic anhydride (30 ml), was treated with boron trifluoride etherate (2 ml) and the reaction mixture was warmed at ca. 60 °C for 1 h when the yellow precipitate dissolved. The cooled reaction mixture was poured onto ice (100 g) and the product collected, washed with water, and dried. It crystallized from chloroform–ether as red needles: 2.0 g (52%); mp 185–186 °C dec (lit.[9] mp 185–186 °C); ir (KBr) 1690, 1590 cm^{-1} (CO); NMR ($CDCl_3$) δ 3.75–4.01 and 4.08–4.33 (AB d, 2, J = 16.5 Hz, $-CH_2-$), 7.48 (m, 10, aromatic); $M^{\cdot+}$ 388 (5).

Anal. Calcd for $C_{18}H_{12}O_2S_4$: C, 55.67; H, 3.12. Found: C, 55.51; H, 3.19.

Cycloaddition Reactions of *anhydro*-2-Aryl-4-hydroxy-1,3-dithiolium Hydroxides. A. With Acetylenic Dipolarophiles. The mesoionic compound (**2**, R = Ph; R^1 = H) (1.94 g, 0.01 mol) and dimethyl acetylenedicarboxylate (1.42 g, 0.01 mol) in anhydrous benzene (50 ml) were heated under reflux for 3 h. After evaporation of the benzene, the crystalline residue was chromatographed on neutral alumina using chloroform as eluent. Dimethyl 2-phenylthiophene-3,4-dicarboxylate (**5**, R = Ph; R^1 = H; R^2 = $COOCH_3$) crystallized from chloroform–petroleum ether (bp 30–60 °C) as cream needles: 1.1 g (40%); mp 70–71 °C; ir (KBr) 1725 cm^{-1} (CO); λ_{max} (CH_3OH) 230 nm (log ϵ 4.28), 275 (3.91); NMR ($CDCl_3$) δ 3.81 (s, 3, 4-$COOCH_3$), 3.83 (s, 3, 3-$COOCH_3$), 7.43 (m, 5, aromatic), 7.98 (s, 1, H_5); $M^{\cdot+}$ 276 (38).

Anal. Calcd for $C_{14}H_{12}O_4S$: C, 60.87; H, 4.38. Found: C, 60.83; H, 4.52.

Dimethyl 2-*p*-methoxyphenylthiophene-3,4-dicarboxylate (**5**, R = *p*-$CH_3OC_6H_4$; R^1 = H; R^2 = $COOCH_3$) obtained from **2** (R = *p*-$CH_3OC_6H_4$; R^1 = H) as above, separated as cream needles from chloroform–petroleum ether: 47%; mp 100–101 °C; ir (KBr) 1725, 1720 cm^{-1} (CO); λ_{max} (CH_3OH) 240 nm (log ϵ 4.41), 275 (4.83); NMR ($CDCl_3$) δ 3.83 (s, 6, 3- and 4-$COOCH_3$), 3.85 (OCH_3), 6.83–6.98 (AB d, 2, J = 9.0 Hz, aromatic), 7.36–7.51 (AB d, 2, J = 9.0 Hz, aromatic), 7.90 (s, 1, H_5); $M^{\cdot+}$ 306 (70).

Anal. Calcd for $C_{15}H_{14}O_5S$: C, 58.82; H, 4.61. Found: C, 58.70; H, 4.49.

Dimethyl 2-*p*-chlorophenylthiophene-3,4-dicarboxylate (**5**, R = *p*-ClC_6H_4; R^1 = H; R^2 = $COOCH_3$), obtained from **2** (R = *p*-ClC_6H_4; R^1 = H), was chromatographed on Kieselgel g using chloroform as eluent. It crystallized from petroleum ether as pale cream prisms: 44%; mp 80–82 °C; ir (KBr) 1725, 1710 cm^{-1} (CO); λ_{max} (CH_3OH) 233 nm (log ϵ 4.36), 275 (4.03); NMR ($CDCl_3$) δ 3.86 (s, 3, 4-$COOCH_3$), 3.90 (s, 3, 3-$COOCH_3$), 7.42 (s, 4, aromatic), 8.0 (s, 1, H_5); $M^{\cdot+}$ 310 (78).

Anal. Calcd for $C_{14}H_{11}ClO_4S$: C, 54.11; H, 3.57. Found: C, 54.24; H, 3.57.

3,4-Dibenzoyl-2-phenylthiophene (**5**, R = Ph; R^1 = H; R^2 = COPh) prepared from **2** (R = Ph; R^1 = H) and dibenzoylacetylene after chromatography on silica gel ($CHCl_3$) afforded cream prisms from chloroform–petroleum ether (bp 30–60 °C): 68%; mp 160–161 °C; ir (KBr) 1670, 1645 cm^{-1} (CO); λ_{max} (CH_3OH) 255 nm (log ϵ 4.62); NMR ($CDCl_3$) δ 8.2–8.0 (m, 15, aromatic), 7.83 (s, 1, H_5); $M^{\cdot+}$ 368 (95).

Anal. Calcd for $C_{24}H_{16}O_2S$: C, 78.25; H, 4.38. Found: C, 78.44; H, 4.19.

B. Olefinic Dipolarophiles. The mesoionic compound **2** (R = Ph; R^1 = H) (0.5 g) and *N*-phenylmaleimide (0.50 g) in dry benzene (100 ml) were heated under reflux for 6 h. After evaporation of the benzene, the residue was chromatographed on Kieselgel g using chloroform as eluent. The adduct (**8**, R = Ph) crystallized from chloroform–ether as colorless needles: 53%; mp 191–193 °C; ir (KBr) 3080, 3020, 2960, 2950, 1730 cm^{-1} (C=O); λ_{max} (CH_3OH) 200 nm (log ϵ 4.91), 215 sh (4.27); NMR (Me_2SO-d_6) δ 3.93 (dd, 1, J_{AB} = 6.6, J_{BC} = 1.0 Hz, H_5), 4.29 (AB d, 1, J_{AB} = 6.6 Hz, H_6), 4.88 (d, 1, J_{BC} = 1.0 Hz, H_4), 7.58–7.13 (m, 10, aromatic); mass spectrum *m/e* (rel intensity) 307 (42), 160 (100).

Anal. Calcd for $C_{19}H_{13}NO_3S_2$: C, 62.13; H, 3.57; N, 3.81. Found: C, 62.00; H, 3.50; N, 3.70.

The corresponding 2-*p*-methoxyphenyl analogue (**8**, R = *p*-$CH_3OC_6H_4$), obtained from **2** (R = *p*-$CH_3OC_6H_4$; R^1 = H), crystallized from chloroform–ether as colorless needles: 60%; mp 173–176 °C; ir (KBr) 1780, 1710, 1610 cm^{-1} (CO); λ_{max} (CH_3OH) 198 nm (log ϵ 4.66), 223 (4.33); NMR ($CDCl_3$) δ 3.8 (s, 3, OCH_3), 3.9 (dd, 2, J_{AB} = 6.5, J_{BC} = 1.0 Hz, H_5), 4.25 (d, 1, J_{AB} = 6.5 Hz, H_6), 4.85 (d, 1, J_{BC} = 1.0 Hz, H_4), 7.53–6.87 (m, 9, aromatic); mass spectrum *m/e* (rel intensity) 365 (4), 337 (82), 190 (100).

Anal. Calcd for $C_{20}H_{15}NO_4S_2$: C, 60.45; H, 3.81; N, 3.53. Found: C, 60.45; H, 3.81; N, 3.53.

The 2-*p*-chlorophenyl analogue (**8**, R = *p*-ClC_6H_4), prepared from **2** (R = *p*-ClC_6H_4; R^1 = H), crystallized from chloroform–ether as colorless prisms: 58%; mp 205–207 °C; ir (KBr) 1780, 1710, 1600 cm^{-1} (CO); λ_{max} (CH_3OH) 200 nm (log ϵ 4.61), 223 (4.34); NMR (Me_2SO-d_6) δ 5.18 (dd, 1, J_{AB} = 6.5, J_{BC} = 1.0 Hz, H_5), 4.73 (ABd, 1, J_{AB} = 6.5 Hz, H_6), 5.16 (d, 1, J_{BC} = 1.0 Hz, H_4), 7.78–7.08 (m, 9, aromatic); mass spectrum *m/e* (rel intensity) 343 (21), 341 (55), 196 (40), 194 (100).

Anal. Calcd for $C_{19}H_{12}ClNO_3S_2$: C, 56.78; H, 3.01; N, 3.49. Found: C, 56.64; H, 3.04; N, 3.36.

The mesoionic compound **2** (R = Ph; R^1 = H) (1.94 g) and acrylonitrile (100 ml) were refluxed for 3 h, the excess acrylonitrile removed in vacuo, and the residue chromatographed on silica gel ($CHCl_3$). The 1:1 adduct, 6-α-cyano-1-phenyl-2,7-dithiabicyclo[2.2.1]heptan-3-one[26] (**9**, R = CN) crystallized from chloroform–petroleum ether as colorless prisms: 53%; mp 105 °C; ir (KBr) 3010, 2960, 2250 (C≡N), 1710 cm^{-1} (C=O); λ_{max} (CH_3OH) 200 nm (log ϵ 4.33); NMR ($CDCl_3$) δ 7.49 (m, 5, aromatic), 4.54 (dd, 1, H_4), 4.05 (dd, 1, $H_{6\alpha}$), 3.00 (m, 1, $H_{5\alpha}$), 2.76 (m, 1, $H_{5\beta}$), $J_{4,5\alpha}$ = 1.3, $J_{4,5\beta}$ = 4.7, $J_{5\alpha,6\alpha}$ = 7.7, $J_{5\beta,6\alpha}$ = 4.0 Hz; $M^{\cdot+}$ 247 (4).

Anal. Calcd for $C_{12}H_9NOS_2$: C, 58.30; H, 3.67; N, 5.67. Found: C, 58.44; H, 3.62; N, 5.60.

The mesoionic compound **2** (R = Ph; R^1 = H) (1.94 g) and ethyl acrylate (100 ml) were refluxed for 1 h, the excess ethyl acrylate removed in vacuo, and the residue was then chromatographed on silica gel ($CHCl_3$). The 1:1 adduct 6-carboethoxy-1-phenyl-2,7-dithiabicyclo[2.2.1]heptan-3-one (**9**, R = $COOC_2H_5$) crystallized from chloroform–petroleum ether as colorless needles: 57%; mp 84–86 °C; ir (KBr) 3070, 3045, 3100, 2980, 2945, 2920, 2880, 1730 br cm^{-1} (C=O); λ_{max} (CH_3OH) 200 nm (log ϵ 4.60); NMR ($CDCl_3$) δ 7.36 (m, 5, aromatic), 4.43 (dd, 1, H_4), 3.94 (dd, 1, $H_{6\alpha}$), 3.73 (q, 2, J = 7.0 Hz, CH_2), 2.70 (m, 2, H_5), 0.76 (t, 3, J = 7.0 Hz), $J_{H_4,H_{5\alpha}}$ = 1.7, $J_{4,5\beta}$ = 4.0, $J_{5\alpha,5\beta}$ = 7.5, $J_{5\alpha,6\alpha}$ = 7.0, $J_{5\beta,6\alpha}$ = 5.0 Hz; $M^{\cdot+}$ 294 (4).

Anal. Calcd for $C_{14}H_{14}O_3S_2$: C, 57.14; H, 4.76. Found: C, 57.28; H, 4.79.

C. Azirines. 2,3-Diphenylazirine (0.965 g, 5.0 mmol) and **2** (R = R^1 = Ph) (1.35 g, 5.0 mmol) were refluxed in xylene for 72 h. After removal of the solvent the residual dark oil was chromatographed on silica gel using benzene as eluent. Recrystallization of the major fraction from ethanol gave **11** (R = Ph) as colorless prisms: 0.96 g (2.07 mmol) (41%); mp 195 °C; ir (KBr) 1690 cm^{-1}; λ_{max} (CH_3OH) 244 nm (log ϵ 4.40); NMR ($CDCl_3$) δ 8.18–6.76 (m, 20, aromatic), 5.66 (s, 1, H); $M^{\cdot+}$ 463 (4).

Anal. Calcd for $C_{29}H_{21}NOS_2$: C, 75.13; H, 4.57; N, 3.02. Found: C, 74.91; H, 4.61; N, 3.07.

The endo isomer **12** (R = Ph), mixed with the exo isomer above, was finally separated by PLC and purified by recrystallization from ethanol, forming colorless plates: 0.09 g (0.2 mmol), 4%; mp 229 °C; ir (KBr) 1690 cm^{-1} (CO); NMR ($CDCl_3$) δ 8.21–6.73 (m, 20, aromatic), 5.95 (s, 1, H); $M^{\cdot+}$ 463 (3).

3-Methyl-2-phenylazirine (1.31 g, 10 mmol) and **2** (R = R^1 = Ph) (2.70 g, 10 mmol) were refluxed in *p*-xylene (50 ml) for 11 h. Removal of solvent gave a brown oil which was chromatographed over silica gel and eluted with benzene–hexane (4:1) to give a colorless residue, recrystallizing from ethanol as fine, colorless prisms of **11** and **12** (R = CH_3): 2.27 g (5.66 mmol), 57%; mp 123–125 °C; ir (KBr) 1680 cm^{-1} (CO); λ_{max} (CH_3OH) 243 nm (log ϵ 4.09); NMR ($CDCl_3$) δ 8.16–6.96 (m, 15, aromatic), 4.45 and 3.71 (q, 1, J = 6.0 Hz, H), 1.35 and 1.11 (d, 3, J = 6.0 Hz, CH_3); $M^{\cdot+}$ 401 (1).

Anal. Calcd for $C_{24}H_{19}NOS_2$: C, 71.81; H, 4.77; N, 3.49. Found: C, 71.61; H, 4.72; N, 3.44.

Oxidation of 11 (R = Ph) with *m*-Chloroperbenzoic Acid. A solution of the adduct (0.1 g, 0.21 mmol) in dichloromethane (10 ml) was treated with *m*-chloroperbenzoic acid (0.045 g, 0.25 mmol) and the mixture was stirred for 16 h. The precipitate was filtered, and the filtrate was washed with water (2 × 10 ml) and dried over sodium sulfate. The solvent was removed and the residue was recrystallized from chloroform–ethanol to give fine, colorless needles of **13** (R = Ph): 0.054 g (0.11 mmol), 53%; mp 214 °C; ir (KBr) 1690 (CO), 1177 cm^{-1} (SO); NMR ($CDCl_3$) δ 8.16–6.90 (m, 20, aromatic), 5.76 (s, 1, H); $M^{\cdot+}$ 479 (1).

Anal. Calcd for $C_{29}H_{21}NO_2S_2$: C, 72.64; H, 4.42; N, 2.92. Found: C, 72.68; H, 4.48; N, 2.89.

Oxidation of 11–12 (R = CH_3) with *m*-Chloroperbenzoic Acid. The mixture of adducts (1.0 g, 0.25 mmol) was treated in dichloromethane (10 ml) with *m*-chloroperbenzoic acid (0.51 g, 3 mmol) in dichloromethane (5 ml). The mixture was stirred for 20 h and the precipitated solid was filtered. Workup of the filtrate as above gave an oil which crystallized from chloroform–ethanol as colorless plates of **14** (R = CH_3): 0.52 g (0.12 mmol), 50%; mp 193 °C; ir (KBr) 1700 (CO), 1085 cm^{-1} (SO); NMR ($CDCl_3$) δ 8.06–7.13 (m, 15, aromatic), 5.48 (q, 1, J = 6.0 Hz, H), 1.18 (d, 3, J = 6.0 Hz, CH_3); $M^{\cdot+}$ 417 (1).

Anal. Calcd for $C_{24}H_{19}NO_2S_2$: C, 69.05; H, 4.59; N, 3.36. Found: C, 69.23; H, 4.66; N, 3.36.

Registry No.—**2** (R = Ph; R^1 = H), 58426-74-7; **2** (R = *p*-$CH_3OC_6H_4$; R^1 = H), 58426-75-8; **2** (R = *p*-ClC_6H_4; R^1 = H), 58426-76-9; **2** (R = Ph; R^1 = $COCH_2SCSPh$), 58426-77-0; **2** (R = R^1 = Ph), 58426-78-1; **3** (R = Ph; R^1 = H), 942-91-6; **3** (R = *p*-$CH_3OC_6H_4$; R^1 = H), 38204-31-8; **3** (R = *p*-ClC_6H_4; R^1 = H), 38204-36-3; **5** (R = Ph; R^1 = H; R^2 = $COOCH_3$), 23436-87-5; **5** (R = *p*-$CH_3OC_6H_4$; R^1 = H; R^2 = $COOCH_3$), 23436-88-6; **5** (R = *p*-ClC_6H_4; R^1 = H; R^2 = $COOCH_3$), 58426-79-2; **5** (R = Ph; R^1 = H; R^2 = COPh), 58426-80-5; **8** (R = Ph), 58426-81-6; **8** (R = *p*-$CH_3OC_6H_4$), 58426-82-7; **8** (R = *p*-ClC_6H_4), 58426-83-8; **9** (R = CN), 58426-84-9; **9** (R = $COOC_2H_5$), 58426-85-0; **11** (R = Ph), 58426-86-1; **11** (R = CH_3), 58426-87-2; **12** (R = Ph), 58462-43-4; **12** (R = CH_3), 58462-44-5; **13** (R = Ph), 58426-88-3; **14** (R = CH_3), 58426-89-4; dimethyl acetylenedicarboxylate, 762-42-5; dibenzoylacetylene, 1087-09-8; *N*-phenylmaleimide, 941-69-5; acrylonitrile, 107-13-1; ethyl acrylate, 140-88-5; 2,3-diphenylazirine, 16483-98-0; 3-methyl-2-phenylazirine, 16205-14-4.

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Preparation and Physical and Chemical Properties of "Free" Sulfilimines[1]

Toshiaki Yoshimura and Tetsuo Omata[†]

Department of Applied Chemistry, Faculty of Engineering, Osaka City University, Sugimoto-cho, Osaka, Japan

Naomichi Furukawa* and Shigeru Oae

Department of Chemistry, The University of Tsukuba, Sakuramura, Niihari-gun, Ibaraki, Japan

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N-*p*-Tosylsulfilimines, when dissolved in concentrated sulfuric acid, are converted to the corresponding *p*-toluenesulfonic acid salts of sulfilimines which upon treatment with alkali give "free" sulfilimines in good yields. Diaryl sulfilimines are relatively stable crystalline compounds, while dialkyl or alkyl aryl derivatives are unstable and decompose readily at room temperature to form the corresponding sulfides and ammonia. The structure of "free" sulfilimine was identified by spectroscopic and elemental analyses. Some of the interesting chemical behavior of "free" diphenylsulfilimines is described.

The acid-catalyzed hydrolysis of *N*-*p*-tosylsulfilimine is known to give the corresponding sulfoxide in high yield.[2] The mechanism for the hydrolysis has been explored kinetically by Kucsmann and his co-workers[3] using *N*-arylsulfonyl alkyl aryl sulfilimines in moderately concentrated aqueous sulfuric acid or perchloric acid. On the basis of the kinetic investigations, the reaction mechanism for the hydrolysis was explained in terms of the nucleophilic attack of water on the positively polarized S(III) atom of the protonated sulfilimine. Meanwhile, we found recently that the treatment of *N*-*p*-tosylsulfilimines with concentrated sulfuric acid gave the corresponding "free" sulfilimine nearly quantitatively.[4]

Earlier methods of preparation of free sulfilimines have been reported by Appel[5] from dialkyl or p,p'-dimethoxydiphenyl sulfide with chloramine or hydroxylamine sulfate. Similarly, Lambert and his co-workers[6] prepared pentamethylenesulfilimine and presented spectroscopic data. Recently Tamura et al.[7] also found a new method which involves treatment of the sulfides and *O*-mesitylenesulfonyl hydroxylamine. More recently, a method which uses diaryl alkoxy sulfurane and ammonia has been described by Martin.[8] However, each of these reactions has some shortcomings for a general synthetic procedure to prepare free sulfilimines. We have now found that any kind of *N*-*p*-tosylsulfilimine can be synthesized readily under certain set conditions from the corresponding sulfides and chloramine-T and their free sulfilimines are readily obtained as salts simply by dissolving them in concentrated sulfuric acid. This synthetic method is the first general procedure for the preparation of varied sulfilimines in large quantities; we now present the details of this procedure and a few pertinent physical and chemical characteristics of the sulfilimines.

Results and Discussion

Diaryl Sulfilimines. Cleavage of diphenyl-*N*-tosylsulfilimine (I) was carried out in 95% sulfuric acid at room temperature. After quenching in ice, the tosylate salt III could be extracted with chloroform. The free sulfilimine (II) crystallized on basifying a solution of III. The imine II has a strong ir absorption band at 940 cm^{-1} which is assigned as –S–N– bond, while other strong absorption bands appear at 2350 (OH) and 3120 cm^{-1} (NH), respectively. The NMR signals of II are δ 7.20–7.70 (10 H, phenyl), 2.1 ppm (1.7 H, NH and OH). The mass spectrum of II was identical with that of diphenyl sulfide; the parent peak due to the free sulfilimine did not appear at all, indicating that the S–N bond of II is weak and is cleaved readily.

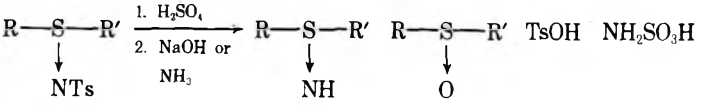
The structure of II was confirmed by treatment with tosyl chloride under alkaline condition to give the starting *N*-*p*-tosylsulfilimine (I) quantitatively. Furthermore, II was hydrolyzed to diphenyl sulfoxide upon heating at 65 °C for 3 h in 20% aqueous sulfuric acid solution. However, II was stable at even relatively strong alkaline conditions and did not react at all in aqueous 20% sodium hydroxide solution at an elevated temperature. The reactions are summarized in Scheme I.

Data for the cleavage of other diaryl *N*-*p*-tosylsulfilimines are summarized in Table I.

Preparation of Alkyl Aryl and Dialkyl Sulfilimines.

[†] Central Institute of Ube Chemical Co., Ube, Japan.

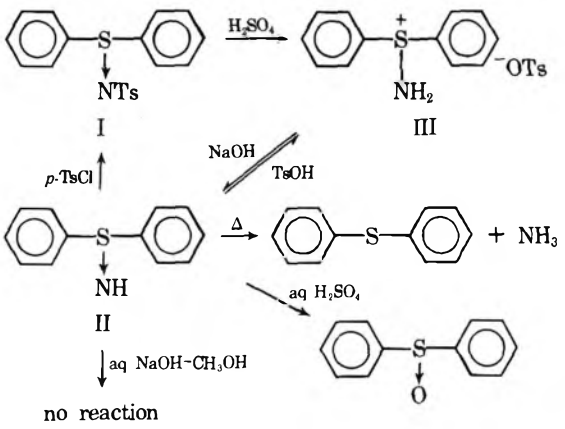
Table I. Products and Yields in the Reaction of *N*-*p*-Tosylsulfilimine with Concentrated Sulfuric Acid



Run	R	R′	Reaction condition r[a]	Temp	Time		Product yields, % II (mp, °C)	IV	V	VI
1	C_6H_5	C_6H_5	2	r.t.	10 min	B	90 (74)[b]			
2	C_6H_5	C_6H_5	5	r.t.	24 h	B		95		
3	C_6H_5	C_6H_5	1	r.t.	24 h	A	24	51		70
4	p-$CH_3C_6H_4$	C_6H_5	2	r.t.	10 min	B	95 (54.5–55.5)[c]			
5	o-$CH_3C_6H_4$	C_6H_5	2	r.t.	10 min	B	97 (83.5–84.5)[c]			
6	p-ClC_6H_4	C_6H_5	2	r.t.	10 min	B	77 (48–49)[c]			
7	m-ClC_6H_4	C_6H_5	2	r.t.	10 min	B	(35–36)[c]			
8	p-$NO_2C_6H_4$	C_6H_5	2	r.t.	10 min	B	95 (98–99)[c]			
9	o-$NO_2C_6H_4$	C_6H_5	2	r.t.	10 min	B	79 (104–104.5)[c]			
10	CH_3	C_6H_5	2	r.t.	5 min	B		97	55	
11	CH_3	C_6H_5	2	r.t.	5 min	A	95 (112–112.5)[d]			
12	CH_3	C_6H_5	1	r.t.	15 min	A		90		83
13	CH_3	p-$CH_3C_6H_4$	2	r.t.	5 min	A	95 (158–159)[d]			
14	C_2H_5	C_6H_5	2	40	15 min	A	95 (90–91)[d]		58	
15	C_2H_5	C_6H_5	2	40	15 min	B		96		
16	c-C_3H_5	p-$CH_3C_6H_4$	2	40	15 min	A	95 (138–139)[d]			
17	CH_3	CH_3	2	40	10 min	A	95 (103–104)[d,e]			
18	C_2H_5	C_2H_5	2	40	10 min	A	95 (110–111)[d]			
19	$-(CH_2)_5-$		2	40	15 min	A	95 (191)		72	
20	$-(CH_2)_5-$		1	r.t.	48 h	A		30[f]		96

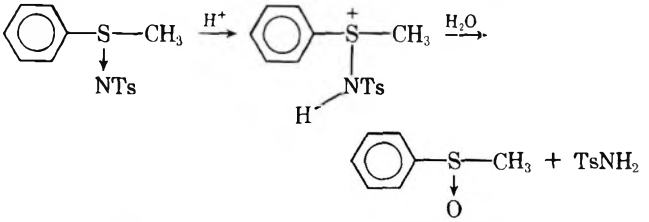
[a] Method A, the acid solution was quenched in cold ether; B, the acid solution was poured onto ice–water. r = ratio, H_2SO_4 (ml)/I (g). [b] Monohydrate. [c] Anhydrous. [d] As picrate. [e] Lit. mp. 111 °C.[5] [f] Corresponding sulfide (20%) was obtained as other product.

Scheme I



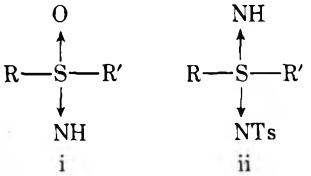
Although diaryl sulfilimines can be prepared readily as illustrated in the case of diphenyl-*N*-*p*-tosylsulfilimine, similar treatment of *N*-*p*-tosyl dialkyl or alkyl aryl sulfilimines with concentrated sulfuric acid did not give the corresponding free sulfilimines but rather the corresponding sulfoxides (runs 9, 14). However, in these reactions *p*-tosylamide, which is usually the by-product of the direct hydrolysis of the sulfilimine to the sulfoxide, was not isolated at all. This suggests that the formation of the sulfoxide does not occur by direct hydrolysis of the *N*-*p*-tosylsulfilimine but by hydrolysis of the initially formed free sulfilimine when the sulfuric acid solution is quenched with ice–water. To avoid hydrolysis of the free sulfilimine, the sulfuric acid solutions of dialkyl or alkyl aryl sulfilimines were added to cold ethyl ether; the oily material which separated was identified as the bisulfate salts of the respective sulfilimines. The free sulfilimines were obtained by treatment of their acetone–methanol solutions with liquid ammonia (runs 10, 12, 13, 15–18). Generally, dialkyl or alkyl aryl free sulfilimines are unstable and decompose readily to the corresponding sulfides and ammonia. Therefore, these sulfilimines should be converted to the picrates as soon as they are isolated. The yields are summarized in Table I.

Chemical Properties of Free Sulfilimines. Reaction Mechanism. The hydrolysis of aryl methyl *N*-*p*-tosylsulfilimines is known to give the corresponding sulfoxides under both acidic and alkaline conditions.[2a] The stereochemical results indicate that under alkaline conditions, the hydrolysis proceeds by an SN2 reaction at sulfur since the configuration of the sulfoxide obtained is completely inverted. Under acidic conditions, the reactions are not stereospecific and yield the racemized sulfoxides. In acid, therefore, prior S–N bond cleavage must occur before nucleophilic attack on sulfur by a water molecule. Recently, Kucsmann et al.[3] studied the hydrolysis of methyl aryl *N*-*p*-arylsulfonylsulfilimines in aqueous sulfuric acid. Based on the Hammett equation and Bunnett–Olsen's values, they suggested that the hydrolysis proceeded by preequilibrium protonation of the imino nitrogen, followed by rate-determining nucleophilic attack of a water molecule. ^{18}O-Labeled sulfoxides, treated under



aqueous acidic conditions, undergo ^{18}O exchange with the medium even in concentrated sulfuric acid.[9] All these data show clearly that either S(III)–N or S(III)–O bond cleavage takes place under acidic reaction conditions. However, our new experimental results indicate that the *N*-*p*-tosylsulfilimine undergoes exclusively N–S(IV) bond cleavage upon treatment with concentrated sulfuric acid. The reaction is very facile and complete within a few minutes. A similar N–S(IV) bond cleavage is observed when an *N*-*p*-tosylsulfoximine[10] or sulfone diimine[11] is treated with concentrated sulfuric acid. For

Table II. Ir Stretching Absorption of Sulfilimine[a]

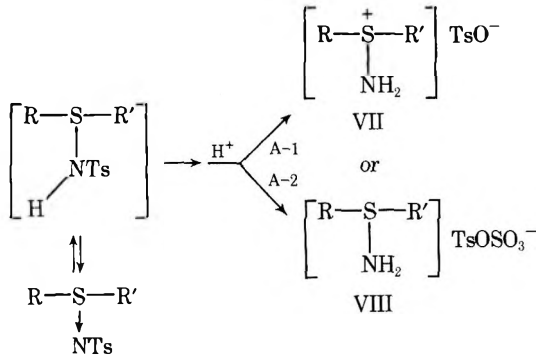


Compd	C_6H_5, C_6H_5	p-$CH_3C_6H_4$	$-(CH_2)_5-$
Free sulfilimine	940	920	900
N-p-Tosylsulfilimine	960	970	985
Sulfoximine[b]	965, 980 1095, 1130	980, 1090[26] 1220	
Sulfone diimine[c]	955, 1080[11]	970, 1050[26]	1010, 1040[11]

[a] In KBr. [b] i. [c] ii.

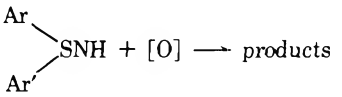
preparation of sulfilimines, the reaction should be carried out with 90–95% sulfuric acid within 10–15 min. The product obtained after longer reaction time (24 h) with 90–95% sulfuric acid was no longer free sulfilimine but the sulfoxide, together with toluenesulfonic acid which was identified as the thiuronium salt (run 2). When I was treated with 80% sulfuric acid at room temperature for 24 h, the N-p-tosylsulfilimine was recovered in 63% yield together with diphenyl sulfoxide (25%). Treatment of I with 50% sulfuric acid led to its complete recovery. Furthermore, when the N-p-tosylsulfilimine was dissolved in a small amount of 95% sulfuric acid or in 98% sulfuric acid and the solution was kept standing for prolonged reaction time (runs 3, 11, 19 in Table I) crystalline sulfamic acid (VI) precipitated.

Apparently, water molecules are in the form of oxonium ions and hence do not participate as a nucleophile in the initial S(IV)–N bond cleavage either by way of A-1 type or A-2 type mechanism. Instead, hydrogen sulfate ion should work as the nucleophile eventually affording the aminosulfonium salt VII or VIII as shown below.



Free sulfilimines thus obtained are generally oily materials except for diaryl derivatives. Therefore, the spectroscopic analysis is recommended for the identification. Free sulfilimines are relatively strong bases (pK_a = 8.5 for diaryl[13]). As shown in the Experimental Section, free sulfilimines have characteristic strong bands at 930–960 cm^{-1} due to S–N stretching band and 3120 cm^{-1} (NH). The position of the characteristic S–N ir band at around 940 cm^{-1} depends on the structure of the sulfilimine. In the case of diaryl compounds, electron-withdrawing substituents shift the band to the longer wavelength while the electron-donating groups do the opposite. In the case of alkyl aryl or dialkyl sulfilimines, the –S–N– absorption bands appear at the region of 900–910 cm^{-1}. The nature of the S–N band, namely whether the bond has semipolar single or double bond character, was discussed earlier with N-p-tosyl derivatives[14] and the former was favored. The several ir bands due to S–N bonds are shown. The characteristic S–N band of free sulfilimines is at lower wavenumber

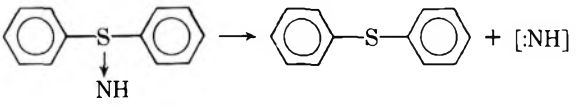
Table III. Oxidation Products of Free Sulfilimine



Ar	Ar′	Oxidant	Products (yields, %)
C_6H_5	C_6H_5	$KMnO_4$	Sulfoximine (95)
p-$CH_3C_6H_4$	C_6H_5	$KMnO_4$	Sulfoximine (95)
p-$NO_2C_6H_4$	C_6H_5	$KMnO_4$	Sulfoximine (80)
C_6H_5	C_6H_5	H_2O_2	Sulfoximine (30), sulfone (20), sulfoxide (20)
C_6H_5	C_6H_5	p-$CH_3C_6H_4CO_3H$	Sulfoximine (40), sulfone (20), sulfoxide (trace)
C_6H_5	C_6H_5	HNO_3	Sulfoxide (95)

than that of N-p-tosyl derivative or sulfoximine. Thus, the S–NH bond is even more semipolar than that of N-p-tosyl derivatives (Table II).

Pyrolysis of Free Sulfilimine. Even though the diaryl free sulfilimines are relatively stable, they decompose readily when heated in situ at 100 °C and afforded the sulfide and ammonia.[15] A detailed account of the pyrolysis of free sulfilimine



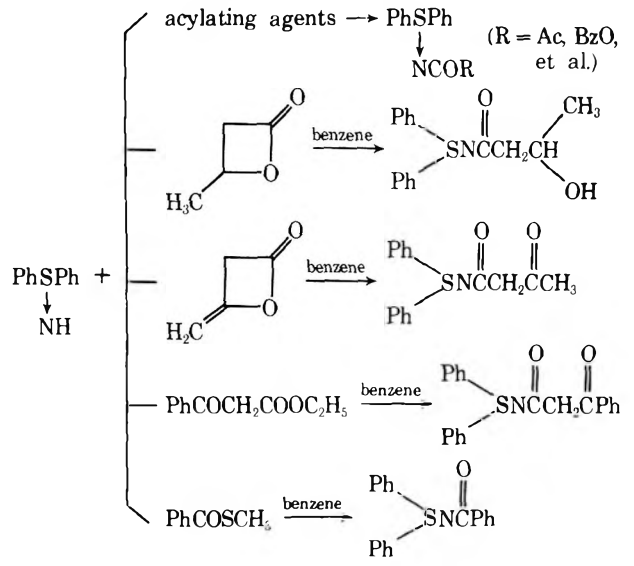
will be described elsewhere. This facile pyrolysis, as compared to that of the corresponding N-p-tosyl derivative, seems to support the conclusion that the S–N bond cleaves very readily forming the sulfide and nitrene which then disproportionates to ammonia.[15,16] The thermal instability of the free sulfilimine is consistent with both the GLC behavior and the mass spectroscopic pattern, which are the same as those of the corresponding sulfide.

Oxidation of Free Sulfilimines. Sulfoximines have hitherto been prepared from the corresponding sulfoxide by either treating with hydrazoic acid[17] or reacting with sulfonyl azide[18] or chloramine-T[19] in the presence of copper. Another alternative procedure is the permanganate oxidation of the N-acylsulfilimine.[20] However, none of these methods is general for the large-scale preparation of all kinds of sulfoximines. Thus it is difficult to prepare the diaryl sulfoximine, while it is dangerous to use a large quantity of toxic and explosive hydrazoic acid. However, because of the interesting pharmacological properties a general and convenient synthetic method of free sulfoximines has long been sought. Thus, the direct oxidation of free sulfilimines was carried out with various oxidizing agents, i.e., potassium permanganate, peracid, or hydrogen peroxide and diaryl sulfoximines having various substituents were successfully obtained in good yields. Generally, the oxidation of free sulfilimine was carried out in methanol solution of the sulfilimine. After the solution was refluxed for 1 h, it was worked up as usual, affording diphenylsulfoximine quantitatively. The sulfoximine was identified by both spectroscopic and elemental analyses. The oxidation was carried out similarly by other oxidizing reagents. The results are summarized in Table III.

As shown in Table III, the best results are obtained when the reaction is carried out with potassium permanganate, while the reaction with peracid or hydrogen peroxide gives a mixture of sulfoximine, sulfone, and sulfoxide. In the case of nitric acid, the sulfoxide was the sole product. This fact indicates that the acid-catalyzed hydrolysis took place during the reaction, affording the sulfoxide.

These sulfoximines have strong ir absorption bands at 940–960 (–S=N–), 1020–1040 (SO), 3300–3400 cm^{-1} (NH).

Scheme II. Reaction of Free Sulfilimine with Acylating Agents



In NMR, there are peaks at 3–4 (–NH–) and 7–8 ppm (phenyl H).

Reaction with Acylating Agents. Previously, we reported a convenient method for the preparation of various *N*-acylsulfilimines from diphenyl free sulfilimine and various acylating agents.[13] Recently, various acylated sulfilimines such as *N*-sulfonyl-,[21] *N*-acyl-,[22] *N*-ethoxycarbonyl-,[22] and *N*-carbamoylsulfilimines[23] were similarly prepared and some of their physical properties are summarized. The preparation of *N*-acyl derivatives from free sulfilimines is very simple. Acylation is completed in a few minutes just by dissolving equimolar amounts of free sulfilimine and acylating agent in benzene at room temperature. Acylating agents used are $(RCO)_2O$, RCOCl, TsCl, RNCO, and EtOC(O)Cl. Furthermore, four- and five-membered lactones, ketene dimer, esters[24] having electron-withdrawing groups such as ethyl acetoacetate or ethyl benzoylacetate, and thioesters also react with free sulfilimines and afforded the *N*-acyl substituted sulfilimines as shown in Scheme II. The *N*-acylsulfilimines having either a hydroxy or a carbonyl group in the molecules are not known and therefore this method is a convenient synthetic procedure for the preparation of such sulfilimine derivative.

The products, their yields, and some spectral data are summarized in the Experimental Section.

Experimental Section

***N*-*p*-Tosylsulfilimines.** All the sulfilimines were prepared by the Mann–Pope reaction by allowing the sulfides to react with chloramine-T.[25]

***S,S*-Diphenylsulfilimine (II). Method A.** Diphenyl-*N*-*p*-tosylsulfilimine (1 g, 0.28 mmol) was dissolved in 1 ml of concentrated sulfuric acid (95% commercial) at room temperature. The solution was kept for 10 min and then poured onto ice. The oily product precipitated out immediately. The aqueous solution was extracted with chloroform. After chloroform was removed, the residue solidified to afford quantitatively the crystalline product which upon recrystallization from acetone–methanol gave colorless crystals of mp 128.5 °C. The product was identified as iminosulfonium *p*-toluenesulfonic acid salt (III) by the following physical and chemical properties. Anal. Calcd for $C_{19}H_{19}NO_3S_2$: C, 60.45; H, 5.07; N, 3.71. Found: C, 60.83; H, 5.21; N, 3.48.

The salt III was then dissolved in chloroform again and washed with 20% aqueous alkali solution. After the chloroform layer was washed with water and the solution was dried, the solvent was evaporated to obtain a white, crystalline material in 75% yield which was recrystallized from benzene or benzene–hexane, mp 70–71 °C. This compound was identified as the free sulfilimine monohydrate. This sulfilimine (0.077 g) and *p*-toluenesulfonic acid (0.067 g) were dissolved in a drop of methanol and acetone was added to this solution. The melting point (128.5 °C) and ir spectrum were identical with those of the original salt III.

Method B. Diphenyl-*N*-*p*-tosylsulfilimine (25 g, 0.07 mol) was dissolved in 40 ml of 95% sulfuric acid. As soon as all the sulfilimine was dissolved, the solution was poured onto ice, made alkaline with aqueous sodium hydroxide solution, and then extracted with chloroform. Chloroform was evaporated at reduced pressure. The residue was dissolved again in 180 ml of 3% sulfuric acid. The solution was decolorized by charcoal. Then the solution was made alkaline. The crystalline precipitates were collected by filtration. Thus, diphenylsulfilimine (14 g) was obtained (90%).

Similarly the following sulfilimines were prepared.[27]

Phenyl-*p*-tolylsulfilimine: mp 54.5–55.5 °C; (KBr) 3170, 930 cm^{-1}; NMR ($CDCl_3$) δ 7.2–7.8 (m, 9 H, phenyl H), 2.40 (s, 3 H, CH_3), 1.7 ppm (s, 1 H, NH). Anal. Calcd for $C_{13}H_{13}NS$: C, 72.52; H, 6.08; N, 6.51. Found: C, 71.69; H, 6.19; N, 6.71.

Phenyl-*o*-tolylsulfilimine: mp 83.5–84.5 °C; (KBr) 3170, 930 cm^{-1}; NMR ($CDCl_3$) δ 7.1–7.8 (m, 9 H, phenyl H), 2.39 (s, 3 H, CH_3), 1.35 ppm (s, 1 H, NH). Anal. Calcd for $C_{13}H_{13}NS$: C, 72.52; H, 6.08; N, 6.51. Found: C, 73.16; H, 6.19; N, 6.21.

Phenyl-*p*-chlorophenylsulfilimine: mp 48–49 °C; ir (KBr) 3140, 935 cm^{-1}; NMR ($CDCl_3$) δ 7.2–7.7 (m, 9 H, phenyl), 1.4 ppm (s, 1 H, NH). Anal. Calcd for $C_{12}H_{10}NCl$: C, 61.14; H, 4.28; N, 5.94. Found: C, 61.02; H, 4.33; N, 5.92.

Phenyl-*m*-chlorophenylsulfilimine: mp 35–36 °C; ir (KBr) 3110, 940 cm^{-1}; NMR ($CDCl_3$) δ 7.3–7.7 (m, 9 H, phenyl), 2.0 ppm (s, 1 H, NH). Anal. Calcd for $C_{12}H_{10}NCl$: C, 61.14; H, 4.28; N, 5.94. Found: C, 60.67; H, 4.46; N, 6.17.

Phenyl-*p*-nitrophenylsulfilimine: mp 98–99 °C; ir (KBr) 3150, 940 cm^{-1}; NMR ($CDCl_3$) δ 7.4–8.4 (m, 9 H, phenyl), 2.1 ppm (1 H, NH). Anal. Calcd for $C_{12}H_{10}O_2N_2S$: C, 58.52; H, 4.09; N, 11.37. Found: C, 58.53; H, 4.20; N, 11.17.

Phenyl-*o*-nitrophenylsulfilimine: mp 104–104.5 °C; ir (KBr) 3110, 960 cm^{-1}; NMR ($CDCl_3$) δ 7.2–8.6 (m, 9 H, phenyl), 1.8 ppm (s, 1 H, NH). Anal. Calcd for $C_{12}H_{10}O_2N_2S$: C, 58.52; H, 4.09; N, 11.37. Found: C, 58.67; H, 4.15; N, 11.38.

Methyl-*p*-tolylsulfilimine (Picrate): mp 158–159 °C. Anal. Calcd for $C_{14}H_{14}O_7N_4S$: C, 43.98; H, 3.69; N, 14.65. Found: C, 43.54; H, 3.61; N, 14.37.

Cyclopropyl-*p*-tolylsulfilimine (Picrate): mp 138–139 °C. Anal. Calcd for $C_{16}H_{16}O_7N_4S$: C, 47.06; H, 3.95; N, 13.72. Found: C, 47.35; H, 3.67; N, 13.62.

Pentamethylenesulfilimine (Picrate): mp 191 °C. Anal. Calcd for $C_{11}H_{14}O_7N_4S$: C, 38.15; H, 4.07; N, 16.18. Found: C, 38.22; H, 4.00; N, 16.21.

Methylphenylsulfilimine. The *N*-*p*-tosylsulfilimine (1 g, 0.34 mmol) was dissolved into 2 ml of 95% sulfuric acid. The reaction mixture was poured into well-cooled ethyl ether and immediately formed an oily material, i.e., the sulfuric acid salt of the free sulfilimine from which the free sulfilimine was obtained upon treatment of acetone–methanol solution of the salt with liquid ammonia. The free methyl-*N*-phenylsulfilimine is an oily substance and unstable at room temperature; therefore it was converted to picrate. The picrate was recrystallized from water, mp 112–112.5 °C. Anal. Calcd for $C_{13}H_{12}O_6N_4S$: C, 42.39; H, 3.28; N, 15.21. Found: C, 42.25; H, 3.15; N, 15.29. Besides this, 0.36 g (55%) of *p*-toluenesulfonic acid was isolated from the ether layer.

Reaction of Diphenylsulfilimine with *p*-Tosyl Chloride. Diphenylsulfilimine (0.10 g, 0.5 mmol) and *p*-tosyl chloride (0.10 g) were dissolved in 1 ml of pyridine. After 10 min the solution was poured onto cold water. The aqueous solution was extracted with chloroform, washed with water, and dried over sodium sulfate. After chloroform was removed, the residue was recrystallized from methanol; *N*-*p*-tosylsulfilimine (0.12 g) was obtained in 70% yield, mp 111 °C.

Acidic Hydrolysis of Diphenylsulfilimine. Diphenylsulfilimine (0.20 g, 1 mmol) was dissolved in 1 ml of 20% aqueous sulfuric acid. This solution was heated at 65–70 °C for 3 h and then was cooled at room temperature and extracted with chloroform. The chloroform solution was washed with water and dried over sodium sulfate and chloroform was removed. Diphenyl sulfoxide (0.18 g, 97%) was obtained.

Meanwhile, diphenylsulfilimine (0.20 g) was dissolved in 5 ml of methanol and 5 ml of aqueous 20% sodium hydroxide was added into this solution. The mixture was refluxed for 24 h; however, diphenylsulfilimine was recovered completely.

Pyrolysis of Sulfilimine. Diphenylsulfilimine (0.20 g, 1.0 mmol) was heated at 100 °C in a sealed tube for 6 h. After the reaction, a gaseous product was found to be ammonia which was dissolved in water and identified by Nessler's reagent. The oily material obtained was identified as diphenyl sulfide by ir and GLC.

ESR Measurement. ESR measurements of diphenyl-, phenyl-*p*-tolyl-, and *p*-nitrophenylphenyl-*N*-*p*-tosylsulfilimines were attempted in 95% sulfuric acid. However, no signals were observed.

Oxidation of Sulfilimine by Potassium Permanganate. Diphenylsulfilimine (0.20 g, 1.0 mmol) was dissolved in 15 ml of methanol. To this solution was added 0.5 g of potassium permanganate in 5 ml of water. The suspension was refluxed for 1 h with stirring and the inorganic precipitates were filtered off. After the solvent was evaporated, diphenylsulfoximine was obtained, 0.21 g (100%). Recrystallization from benzene gave a pure compound: mp 104 °C; ir (KBr) 3270 (NH), 1230, 1130, 1095, 980, 965 cm^{-1} (NSO). Other sulfoximines were prepared similarly by treating the corresponding free sulfilimines with potassium permanganate.

Oxidation of Diphenylsulfilimine by *p*-Methylperbenzoic Acid. Diphenylsulfilimine (0.20 g, 1.0 mmol) in 5 ml of methanol was added to 0.15 g of perbenzoic acid in 5 ml of methanol. The solution was kept at room temperature for 24 h until the TLC spot of the free sulfilimine disappeared. The solution was poured into an aqueous alkaline solution and the aqueous solution was extracted with chloroform. The chloroform solution was dried over anhydrous sodium sulfate. After the solvent was removed, an oily material formed, which was chromatographed through a column packed with silica gel. Then diphenylsulfoximine and diphenyl sulfone were obtained in 40 and 20% yield, respectively.

Preparation of Diphenyl-*N*-acylsulfilimine. Diphenyl-*N*-acetylsulfilimine. Diphenylsulfilimine (0.20 g, 1.0 mmol) was dissolved into 5 ml of benzene. To this solution, acetic anhydride (excess) was added at room temperature. After 10 min the benzene solution was washed with water and dried over anhydrous magnesium sulfate. After the solvent was evaporated, the residual oil solidified to white crystals which were recrystallized from ethanol. The yield was 0.22 g (95%): mp 89 °C; ir (KBr) 1575, 1590, 800 cm^{-1}. Anal. Calcd for $C_{14}H_{13}ONS$: C, 69.17; H, 5.35; N, 5.62. Found: C, 69.10; H, 5.38; N, 5.72.

Diphenyl-*N*-benzoylsulfilimine. Treatment of diphenylsulfilimine (0.20 g, 1.0 mmol) with an equimolar amount of benzoyl anhydride under the same reaction condition as above afforded diphenyl-*N*-benzoylsulfilimine in 95% yield: mp 126–127 °C; ir (KBr) 1595, 1550, 805 cm^{-1}. Anal. Calcd for $C_{19}H_{15}ONS$: C, 74.72; H, 4.95; N, 4.95. Found: C, 74.67; H, 4.95; N, 4.54.

***p*-Nitrophenyl-*N*-acetylphenylsulfilimine.** The reaction condition was similar to the above. Yield was 95%: mp 104 °C; ir (KBr) 1610, 1570, 1000 cm^{-1}. Anal. Calcd for $C_{14}H_{12}O_3N_2S$: C, 57.72; H, 4.20; N, 9.72. Found: C, 57.70; H, 3.91; N, 9.16.

Diphenyl-*N*-phthalylsulfilimine. Treatment of diphenylsulfilimine (0.50 g, 2.5 mmol) with phthalic anhydride (0.37 g) under the same reaction condition afforded diphenyl-*N*-phthalylsulfilimine in 95% yield: mp 157–157.5 °C; ir (KBr) 1730, 1580, 1530, 815 cm^{-1}; NMR ($CDCl_3$) δ 7.5–8.0 (*m*, 10 H, phenyl), 8.4–8.7 ppm (*m*, 2 H, phenyl). Anal. Calcd for $C_{20}H_{15}O_3NS$: C, 68.75; H, 4.33; N, 4.01. Found: C, 68.60; H, 4.33; N, 3.94.

Diphenyl-*N*-succinylsulfilimine. The reaction condition was similar to the above: yield 88%; mp 130–131 °C; ir (KBr) 1730, 1608, 1580, 810 cm^{-1}; NMR ($CDCl_3$) τ 7.5–8.0 (m, 10 H, phenyl), 6.35, 6.80 (dd, 2 H, $-CH{=}CH-$). Anal. Calcd for $C_{16}H_{15}O_3NS$: C, 64.20; H, 4.38; N, 4.68. Found: C, 64.26; H, 4.39; N, 4.54.

Diphenyl-*N*-ethylcarboethoxysulfilimine. Diphenylsulfilimine (0.5 g, 2.5 mmol) was dissolved into 5 ml of benzene. To this solution, ethyl chloroformate (0.27 g) was added at room temperature. The solution was kept standing for 1 h. Then the benzene solution was washed with water and dried over magnesium sulfate. After the solvent was evaporated, an oily residue solidified. Diphenyl-*N*-ethylcarboethoxysulfilimine was thus obtained, 0.67 g (89%). The crude crystals were recrystallized from ethanol: mp 91–92 °C; ir (KBr) 1610, 1570, 825 cm^{-1}. Anal. Calcd for $C_{15}H_{15}O_2NS$: C, 65.91; H, 5.53; N, 5.12. Found: C, 66.02; H, 5.52; N, 5.12.

Diphenyl-*N*-(*N'*-ethylcarbamoyl)sulfilimine. The treatment of diphenylsulfilimine with ethyl isocyanate in benzene solution at room temperature afforded diphenyl-*N*-(*N'*-ethylcarbamoyl)sulfilimine in 95% yield: mp 87 °C; ir (KBr) 1605, 1580 cm^{-1}; NMR ($CDCl_3$) 7.3–7.8 (m, 10 H, phenyl), 3.25 (q, 2 H, $-CH_2-$), 1.13 (t, 3 H, CH_3).

Diphenyl-*N*-(*N'*-phenylcarbamoyl)sulfilimine. The sulfilimine was obtained in 95% yield: mp 124–126 °C; ir (KBr) 1608, 1505, 808 cm^{-1}. Anal. Calcd for $C_{19}H_{16}ON_2S$: C, 71.22; H, 5.03; N, 8.74. Found: C, 71.44; H, 5.04; N, 8.85.

Diphenyl-*N*-(*N'*-phenylthiocarbamoyl)sulfilimine. Treatment of sulfilimine with phenyl thioisocyanate under similar conditions as above afforded the sulfilimine in 95% yield: mp 138.5 °C (CH_3Cl–acetone); ir (KBr) 970 cm^{-1}. Anal. Calcd for $C_{19}H_{16}N_2S_2$: C, 67.82; H, 4.79; N, 8.33. Found: C, 67.74; H, 4.77; N, 8.41.

Diphenyl-*N*-(δ-hydroxyvaleroyl)sulfilimine. A mixture of diphenylsulfilimine (1.00 g, 5 mmol) and 1.5 ml of δ-valerolactone in 10 ml of benzene was refluxed for 24 h until the TLC spot of the corresponding free sulfilimine disappeared. After benzene was evaporated, the residual oily material was chromatographed through a silica gel column using chloroform as an eluent. Thus, diphenyl-*N*-(δ-hydroxyvaleroyl)sulfilimine was obtained: 0.69 g (51%); mp 97–99 °C; ir (KBr) 1580, 1560, 805 cm^{-1}; NMR ($CDCl_3$) δ 7.3–8.0 (*m*, 10 H, phenyl), 3.6–4.2 (m, 2 H, OH + $-CH-$), 2.72 (t, 2 H, $-COCH_2CH_2CH-$), 1.90 (t, 2 H, $-COCH_2CH_2CH-$), 1.20 (d, 3 H, CH_3). Anal. Calcd for $C_{17}H_{19}O_2NS$: C, 67.75; N, 6.35; N, 4.65. Found: C, 67.74; H, 6.36; N, 4.60.

Diphenyl-*N*-acetoacetylsulfilimine. Diphenylsulfilimine (0.50 g, 2.5 mmol) was dissolved in 5 ml of benzene. To this solution was added freshly distilled ketene dimer cooling in an ice–water bath. Then benzene was evaporated and a crystalline residue was obtained, 0.60 g (75%). The crude crystals were recrystallized from ethanol–ether: mp 67–68.5 °C; ir (KBr) 1700, 1590, 1570 cm^{-1}; NMR ($CDCl_3$) δ 7.4–8.0 (*m*, 10 H, phenyl), 3.55 (s, 2 H, CH_2), 2.26 (s, 3 H, CH_3). Anal. Calcd for $C_{16}H_{15}O_2NS$: C, 67.34; H, 5.30; N, 4.91. Found: C, 67.46; H, 5.25; N, 4.78.

Reaction with Phenyl Thiobenzoate. Diphenylsulfilimine (0.50 g, 2.5 mmol) was dissolved in 10 ml of benzene. To this was added phenyl thiobenzoate (0.80 g) under cooling in an ice–water bath. After the addition, the solution was kept at room temperature for 1 h. The benzene solution was washed with dilute sodium hydroxide solution and dried over magnesium sulfate. Benzene was removed affording 0.41 g of diphenyl-*N*-benzoylsulfilimine in 60% yield, mp 127 °C.

Reaction with Ethyl Acetoacetate. Diphenylsulfilimine (0.40 g, 2.0 mmol) was mixed with 1 ml of ethyl acetoacetate in 10 ml of benzene. The solution was refluxed for 24 h. Then benzene was evaporated and the residue was separated through a chromatography column of silica gel using chloroform as an eluent. After the solvent was evaporated, *N*-acetoacetylsulfilimine was obtained, 0.22 g (40%), as an oil.

Registry No.—I (R = R' = C_6H_5), 13150-76-0; I (R = *p*-$CH_3C_6H_4$; R = C_6H_5), 24702-37-2; I (R = *o*-$CH_3C_6H_4$; R = C_6H_5), 53897-89-5; I (R = *p*-ClC_6H_4; R' = C_6H_5), 24702-38-3; I (R = *m*-ClC_6H_4; R' = C_6H_5), 58463-51-7; I (R = *p*-$NO_2C_6H_4$; R' = C_6H_5), 24698-06-4; I (R = *o*-$NO_2C_6H_4$; R' = C_6H_5), 58463-52-8; I (R = CH_3; R' = *p*-$CH_3C_6H_4$), 24702-26-9; I (R = c-C_3H_5; R' = *p*-$CH_3C_6H_4$), 58463-53-9; I (R,R' = $-(CH_2)_5-$), 13553-73-6; I (R = CH_3; R' = C_6H_5), 10330-22-0; II (R = R' = C_6H_5), 36744-90-8; II (R = *p*-$CH_3C_6H_4$; R' = C_6H_5), 36744-92-0; II (R = *o*-$CH_3C_6H_4$; R' = C_6H_5), 54615-60-0; II (R = *p*-ClC_6H_4; R' = C_6H_5), 36744-94-2; II (R = *m*-ClC_6H_4; R' = C_6H_5), 58463-54-0; II (R = *p*-$NO_2C_6H_4$; R' = C_6H_5), 36744-95-3; II (R = *o*-$NO_2C_6H_4$, R' = C_6H_5), 54615-61-1; II (R = CH_3; R' = *p*-$CH_3C_6H_4$) picrate, 58463-56-2; II (R = c-C_3H_5; R' = *p*-$CH_3C_6H_4$) picrate, 58463-58-4; II (R,R' = $-(CH_2)_5-$) picrate, 58463-59-5; II (R = CH_3; R' = C_6H_5) picrate, 58463-60-8; III, 58463-61-9; sulfuric acid, 7664-93-9; *p*-tosyl chloride, 98-59-9; potassium permanganate, 7722-64-7; diphenylsulfoximine, 22731-83-5; *p*-methylperbenzoic acid, 937-21-3; diphenyl-*N*-acetylsulfilimine, 42397-41-1; diphenyl-*N*-benzoylsulfilimine, 39149-60-5; benzoyl anhydride, 93-97-0; *p*-nitrophenyl-*N*-acetylphenylsulfilimine, 58463-62-0; diphenyl-*N*-phthalylsulfilimine, 58463-63-1; diphenyl-*N*-succinylsulfilimine, 58485-81-7; diphenyl-*N*-ethylcarboethoxysulfilimine, 39149-62-7; ethyl chloroformate, 541-41-3; diphenyl-*N*-(*N'*-ethylcarbamoyl)sulfilimine, 58463-64-2; ethyl isocyanate, 109-90-0; diphenyl-*N*-(*N'*-phenylcarbamoyl)sulfilimine, 42397-43-3; diphenyl-*N*-(*N'*-phenylthiocarbamoyl)sulfilimine, 58463-65-3; phenyl thioisocyanate, 103-72-0; diphenyl-*N*-(δ-hydroxyvaleroyl)sulfilimine, 58463-66-4; δ-valerolactone, 542-28-9; diphenyl-*N*-acetoacetylsulfilimine, 58463-67-5; phenyl thiobenzoate, 884-09-3; ethyl acetoacetate, 141-97-9.

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(27) All sulfilimines thus obtained have crystalline water but the content of it is not so clear so that some slightly erroneous elemental analyses data were obtained.

Synthesis of [1]Benzothieno[3,2-*d*]-*v*-triazine Derivatives. A Unique Diazonium Ion Cyclization

James R. Beck* and Joseph A. Yahner

Lilly Research Laboratories, Division of Eli Lilly and Company, Greenfield, Indiana 46140

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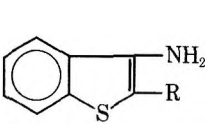
Diazotization of 3-aminobenzo[*b*]thiophene-2-carbonitrile in hydrochloric acid yielded 4-chloro[1]benzothieno-[3,2-*d*]-*v*-triazine. Various derivatives were prepared by nucleophilic displacement using methoxide, methylamine, dimethylamine, hydrazine, and hydroxide ion. The parent heterocycle, [1]benzothieno[3,2-*d*]-*v*-triazine, was obtained by oxidation of the hydrazine derivative.

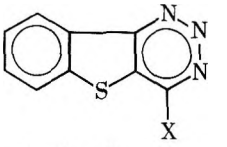
Diazonium ion condensation with an adjacent nucleophilic function to form a five- or six-membered ring has proved valuable for synthesizing various nitrogen heterocycles. Among these are numerous 1,2,3-benzotriazines, including 4-ones from carboxamides,[1] 4-imines from amidines,[2] 3-amino-4-ones from carboxhydrazides,[3] 3-oxides from oximes,[4] and 4-amino-3-oxides from amidoximes.[5] Other examples involving cyclization with nitrogen nucleophiles include the preparation of benzothiatriazine *S,S*-dioxides from sulfonamides[6] and benzotriazoles from amines.[7] Examples of cyclization with carbon nucleophiles are the synthesis of 4-cinnolones from ketones[8] and nitroindazoles from activated methyl functions.[9] Indazole itself has been prepared in high yield from diazotized o-toluidine.[10]

We were unable to find any examples in the literature that involved condensation of a diazonium ion with an adjacent cyano function. Therefore, we were surprised when the product obtained by diazotization of 3-aminobenzo[*b*]thiophene-2-carbonitrile (**1a**)[11] in hydrochloric acid was 4-chloro[1]benzothieno[3,2-*d*]-*v*-triazine (**2a**, 77% yield). The product underwent normal halide displacement with a variety of nucleophiles, including methoxide ion, methylamine, dimethylamine, and hydrazine, to yield the derivatives **2b** (87%), **2c** (70%), **2d** (63%), and **2e** (55%), respectively. Complex mixtures were obtained with ammonia, azide, and excess methyl mercaptan anion, indicating possible triazine ring fission with these nucleophiles. Oxidation of the hydrazine derivative **2e** with mercuric oxide[12] yielded the parent heterocycle **2f** (54%). The ultraviolet spectrum of **2f** was similar to that of **2a** (see Experimental Section).

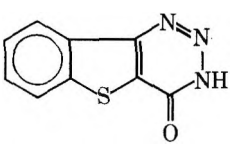
An unequivocal synthesis of **2a** was attempted by, first of all, hydrolyzing **1a** in alcoholic potassium hydroxide to form the carboxamide **1b** (82%). Diazotization of **1b** in sulfuric acid yielded the triazinone **3** (88%).[13] Attempts to prepare **2a** from **3** utilizing standard reagents (phosphorus oxychloride, phosphorus trichloride, and thionyl chloride–DMF) were unsuccessful, apparently owing to the instability of the triazine ring. Nevertheless, a proof of structure was accomplished by treating **2a** with aqueous potassium hydroxide and obtaining a triazinone (79%) identical in all respects with **3**. When **3** was subjected to the same reaction conditions utilized in the formation of **2a** from **1a**, it was recovered unchanged, indicating that it is not an intermediate in that transformation.



1a, R = CN
b, R = $CONH_2$



2a, X = Cl
b, X = OCH_3
c, X = $NHCH_3$
d, X = $N(CH_3)_2$
e, X = $NHNH_2$
f, X = H



3

The scope of this interesting triazine ring closure will receive our further attention. No evidence for the presence of 4-chloro-1,2,3-benzotriazine was found when anthranilonitrile

was diazotized under identical reaction conditions. The only product isolated after chromatography was the corresponding linear triazine (9%) formed by condensation of the diazonium ion with unreacted anthranilonitrile. Similarly, diazotization of 3-amino-4-chloro-2-benzofurancarbonitrile[14] under the same conditions led to a complex mixture.

The fact that both of these aminonitriles failed to undergo the cyclization probably indicates stabilization of the diazotized **1a** intermediate by the sulfur atom. A possible mechanism could involve the intermediacy of an imidoyl chloride,[15] whose geometry would be suitable for condensation with the adjacent diazonium ion.

Experimental Section[16]

3-Aminobenzo[*b*]thiophene-2-carboxamide (1b). A solution containing 4.4 g (25 mmol) of **1a**[11] and 2.2 g of potassium hydroxide in 100 ml of alcohol was refluxed for 4 h. The mixture was cooled and filtered to yield 3.9 g (82%) of product, mp 218–220 °C.

Anal. Calcd for $C_9H_8N_2OS$: C, 56.23; H, 4.19; N, 14.57. Found: C, 56.25; H, 4.30; N, 14.27.

4-Chloro[1]benzothieno[3,2-*d*]-*v*-triazine (2a). To a cold slurry (ice bath) containing 4.4 g (25 mmol) of **1a**,[11] 30 ml of concentrated hydrochloric acid, and 30 ml of acetic acid was added dropwise a solution containing 2.1 g (30 mmol) of sodium nitrite in 20 ml of water. The mixture was warmed to room temperature and stirred for 2 h and then poured into ice water. The solid was collected and crystallized from DMF–water to yield 4.2 g (77%) of product: mp 163–165 °C dec; uv λ_{max} (alcohol) 225 nm (ϵ 26 100), 267 (18 070), 315 (sh).

Anal. Calcd for $C_9H_4ClN_3S$: C, 48.77; H, 1.82; N, 18.96. Found: C, 48.55; H, 1.96; N, 19.08.

4-Methoxy[1]benzothieno[3,2-*d*]-*v*-triazine (2b). A solution containing 2.2 g (10 mmol) of **2a** and 0.7 g (12 mmol) of sodium methoxide in 100 ml of methanol was refluxed for 1 h. The mixture was cooled and filtered to yield 1.9 g (87%) of product, mp 165–167 °C dec.

Anal. Calcd for $C_{10}H_7N_3OS$: C, 55.29; H, 3.25; N, 19.34. Found: C, 55.05; H, 3.47; N, 19.25.

4-(Methylamino)[1]benzothieno[3,2-*d*]-*v*-triazine (2c). Methylamine was bubbled into a refluxing solution of 4.4 g (20 mmol) of **2a** in 100 ml of absolute alcohol for 1 h. The mixture was cooled and the solid was collected. Crystallization from alcohol–water yielded 3.1 g (70%) of product, mp 231–232 °C dec.

Anal. Calcd for $C_{10}H_8N_4S$: C 55.54; H, 3.73; N, 25.91. Found: C, 55.81; H, 4.02; N, 25.93.

4-(Dimethylamino)[1]benzothieno[3,2-*d*]-*v*-triazine (2d). Dimethylamine was bubbled slowly into a solution containing 2.0 g (9 mmol) of **2a** in 50 ml of DMF at 100 °C for 90 min. The mixture was cooled and filtered to yield 1.3 g (63%) of product, mp 207–209 °C dec.

Anal. Calcd for $C_{11}H_{10}N_4S$: C, 57.37; H, 4.38; N, 24.31. Found: C, 57.43; H, 4.61; N, 24.27.

4-Hydrazino[1]benzothieno[3,2-*d*]-*v*-triazine (2e). A solution of 2.5 g (12 mmol) of **2a** and 10 ml of hydrazine hydrate in 75 ml of alcohol was refluxed for 2 h. The mixture was cooled and the solid was collected. Crystallization from DMF–water yielded 1.3 g (55%) of product, mp 194–196 °C dec.

Anal. Calcd for $C_9H_7N_5S$: C, 49.76; H, 3.25; N, 32.24. Found: C, 49.99; H, 3.27; N, 32.43.

[1]Benzothieno[3,2-*d*]-*v*-triazine (2f). A mixture containing 2.1 g (10 mmol) of **2e** and 5.4 g (25 mmol) of mercuric oxide in 130 ml of water was refluxed for 4 h. The slurry was cooled and filtered. The crude solid was triturated with hot ethyl acetate. Filtration and removal of the solvent yielded a residue which was chromatographed on silica gel (Woelm, 250 g) using ethyl acetate–hexane (1:1) as the eluent. The solid obtained was crystallized from alcohol–water to yield 1.0 g (54%) of product: mp 190–191 °C dec; uv λ_{max} (alcohol) 225 nm (ϵ 25 770), 265 (14 810), 320 (sh).

Anal. Calcd for $C_9H_5N_3S$: C, 57.74; H, 2.67; N, 22.44. Found: C, 57.82; H, 2.81; N, 22.41.

[1]Benzothieno[3,2-*d*]-*v*-triazin-4(3*H*)-one (3). Method A. A solution of 2.2 g (10 mmol) of **2a** and 1.0 g of potassium hydroxide in 75 ml of water was refluxed for 30 min. The mixture was cooled and acidified with concentrated hydrochloric acid. The solid was collected and crystallized from DMF–water to yield 1.6 g (79%) of product: mp 179–181 °C dec (lit.[13] mp 180–182 °C); uv λ_{max} (alcohol) 234 nm (ϵ 31 275), 253 (17 575), 320 (6375).

Anal. Calcd for $C_9H_5N_3OS$: C, 53.19; H, 2.48; N, 20.68. Found: C, 53.47; H, 2.62; N, 20.90.

Method B. To a cold mixture (ice bath) of 1.3 g (18 mmol) of sodium nitrite in 30 ml of concentrated sulfuric acid was added dropwise a solution containing 3.5 g (18 mmol) of **1b** in 35 ml of acetic acid. The mixture was stirred for 30 min and then poured into ice water. The crude solid was collected and crystallized from DMF–water to yield 2.3 g (63%) of product, mp 185 °C dec. Concentration of the mother liquors yielded an additional 0.9 g of product, mp 185 °C dec. The combined yield was 3.2 g (88%). This product was identical with that obtained by method A (NMR, ir, and uv spectra).

Acknowledgment. The authors thank Mr. Paul Unger and associates for spectral measurements and Mr. George Maciak and associates for microanalytical data.

Registry No.—**1a,** 34761-14-3; **1b,** 37839-59-1; **2a,** 58374-96-2; **2b,** 58374-97-3; **2c,** 58374-98-4; **2d,** 58374-99-5; **2e,** 58375-00-1; **2f,** 40826-40-2; **3,** 55557-47-6.

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(15) H. Ulrich, "The Chemistry of Imidoyl Halides", Plenum Press, New York, N.Y., 1968, p 66.
(16) Melting points were determined on a Mel-Temp apparatus and are uncorrected.

Oxazolines. XX. Synthesis of Achiral and Chiral Thiiranes and Olefins by Reaction of Carbonyl Compounds with 2-(Alkylthio)-2-oxazolines

A. I. Meyers* and Michael E. Ford[1]

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

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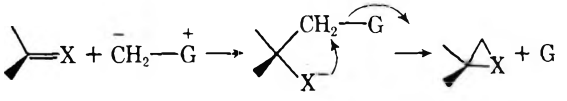
Metalation of 2-(alkylthio)-2-oxazolines (**6–12**) followed by addition of a variety of carbonyl compounds leads to thiiranes **17** in 60–70% yield. The process is also useful for the direct synthesis of alkenes and dienes by extrusion of the sulfur from thiiranes. In many cases a high degree of stereoselectivity is observed in the alkene formation. An asymmetric synthesis of chiral thiiranes has also been achieved providing these substances in 19–32% enantiomeric excess.

Thiiranes, known for over 50 years, have been the subject of several reviews[2] which have dealt mainly with their preparations and reactions. Although reaction of thiiranes with nucleophilic reagents leading to olefins is now a well-known process,[2e,3] the synthetic utility of this transformation has only recently been appreciated.[4,5] From the past literature the preferred route to thiiranes has been by conversion of epoxides and vicinally substituted ethane derivatives.[2,6] Additions of organometallics to thioketones is an interesting route[2d,e] but the availability and inherent instability of thiocarbonyls have deterred this method from further development.

In recent years, a variety of methylene transfer reagents have been cleverly employed[7,8] to convert carbonyl compounds to oxiranes (Scheme I). Thus, sulfur ylides have added

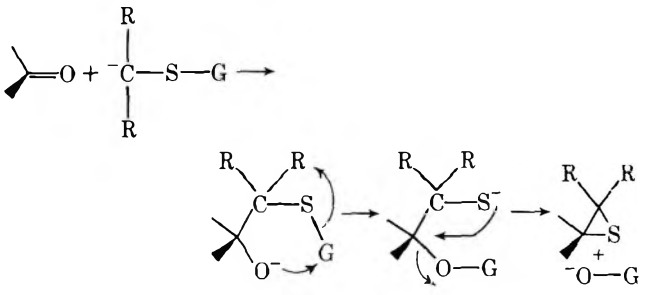
Scheme I



X = O, S, NR; G = SMe_2, $SOMe_2$, $S(NMe_2)OPh$, $S(NTsNa)OPh$

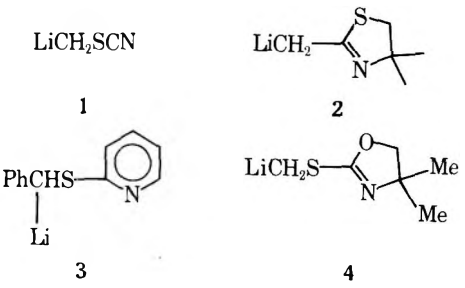
smoothly to carbonyls (X = O) affording a variety of oxiranes. This process would seem to be most attractive for reaching thiiranes if the thiocarbonyls (X = S) were a more accessible functional group. Unfortunately, as mentioned above, this is not the case. A more viable route to thiiranes using carbonyl compounds would be in hand if a thiomethylene transfer reagent ($^-CR_2SG$) were readily accessible (Scheme II). Such a

Scheme II



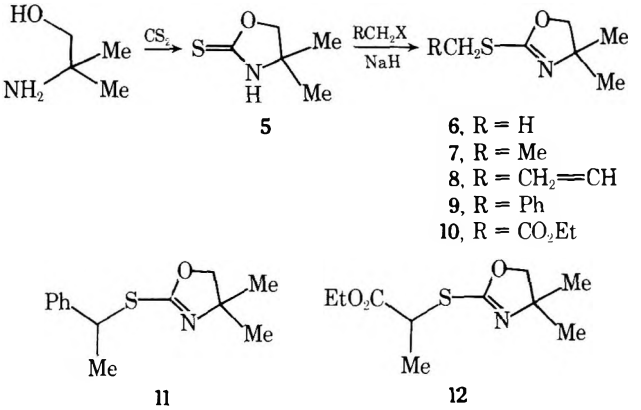
(R = H, alkyl, aryl)

reagent would require a group G which allows ready O for S substitution while also performing as a good leaving group. Several reports have recently appeared utilizing this concept where the thiomethylene transfer group originates from sulfur-stabilized carbanions **1**,[9] **2**,[9,10] **3**,[9] and **4**.[11] The lithio thiocyanate failed to undergo reaction leading to thiiranes whereas **2**, **3**, and **4** indeed gave thiiranes in varying yields.



It is now desirable to fully describe our results using **4** and its homologues as an efficient thiomethylene transfer reagent producing a variety of thiiranes, both achiral and chiral, as well as the conversion of the latter to various olefins. In one instance a chiral olefin was prepared (vide infra). The sequence leading to the 2-(alkylthio)-2-oxazolines **6–12** is shown in Scheme III. Alkylation of oxazolidine-2-thione **5**[12] with various

Scheme III



primary alkyl halides and sodium hydride gave the thioalkyl oxazolines **6–10** whereas metalation of **9** (BuLi) and **10** (LDA) followed by addition of methyl iodide gave **11** and **12**. The yields of **6–12** ranged from 56 to 94% and they are easily prepared in multigram quantities.

Treatment of the 2-alkylthio-2-oxazolines **6**, **8**, **9**, and **11** with *n*-butyllithium (−78 °C, THF) gave the lithio derivative **13** as a yellow-orange solution after 2 h. Addition of a carbonyl compound at −78 °C and allowing the mixture to warm to ambient temperature resulted in the formation of thiiranes **17** in yields ranging from 60 to 70% (Table I). The one-pot process may be depicted as passing through the intermediates **14**, **15**, and **16** in a fashion similar to that reported by Hirai utilizing thiazolines.[13] The sequence outlined in Scheme IV therefore fulfills the general requirements set forth in Scheme II. The ejection of the lithio oxazolidinone **18** as the requisite

Table I. Thiiranes (17) and Olefins (20) from 2-(Alkylthio)-2-oxazolines[a]

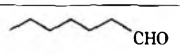
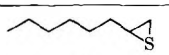
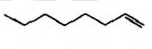
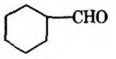
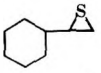
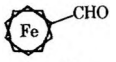
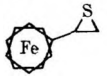
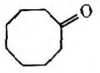
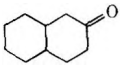
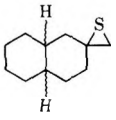
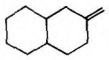
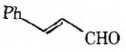
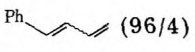
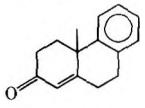
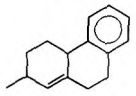
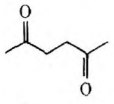
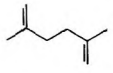
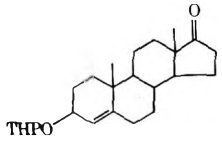
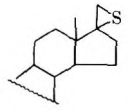
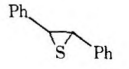
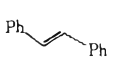
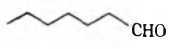
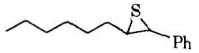
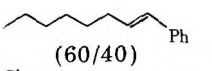
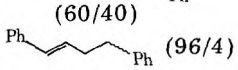
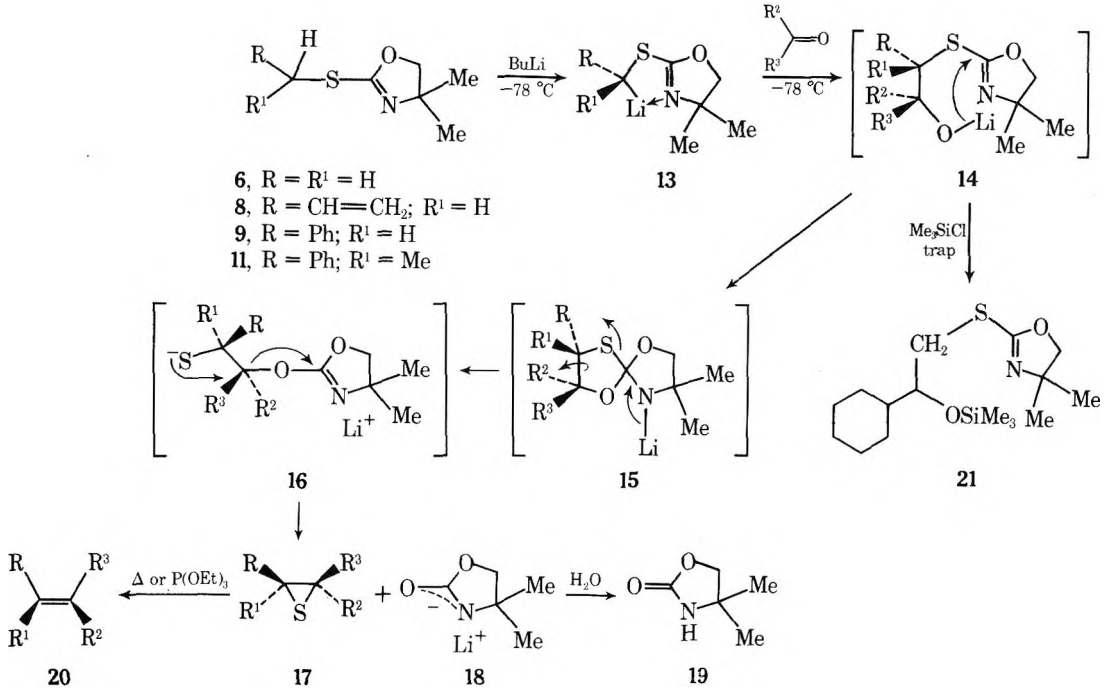
Entry	Oxazoline R	Carbonyl compd	Registry no.	Thiirane 17	Yield,[b] %	Olefin (E/Z)[c]	% yield[b] A[d]	% yield[b] B[e]
1	6 (R = H)		111-71-7		73		64	69
2	6 (R = H)		2043-61-0		78			69
3	6 (R = H)		12093-10-6		68	*f*		
4	6 (R = H)		823-76-7		66	*f*		
5	6 (R = H)		502-49-8		61		65	47
6	6 (R = H)		103-79-7		31 (62)[g]			
7	6 (R = H)		4832-17-1		61		52	
8	6 (R = H)		932-66-1	*h*				42
9	6 (R = H)		14371-10-9	*h*		 (96/4)		46
10	6 (R = H)		529-34-0	*h*				46[i]
11	6 (R = H)		6606-34-4	*h*				48[i]
12	6 (R = H)		110-13-4	*h*				40
13	6 (R = H)		583-60-8		61		56	
14	6 (R = H)		19637-35-5		70	*f*		
15	9 (R = Ph)	PhCHO	100-52-7		71[j]	 (86/14)	81	
16	9 (R = Ph)				64[k]	 (60/40)	75	
17	9 (R = Ph)			*h*		 (96/4)		70
18	9 (R = Ph)			*h*				72
19	11 (R = PhCH(Me))		119-61-9	*h*				62
20	11 (R = PhCH(Me))		712-50-5	*h*		(91/9)		51
21	8 (R = CH=CH$_2$)	PhCHO		*h*		(96/4)		62
22	8 (R = CH=CH$_2$)			*h*		(97/3)		47

Table I (*Footnotes*)

[a] Literature references for all known compounds and physical data for all new compounds are given in the Experimental Section. [b] Purified by chromatography and/or bulb-to-bulb distillation (see Experimental Section for typical procedural details). Products are >95% pure by VPC, NMR, and TLC. [c] Mixtures determined by VPC using a Hewlett-Packard 5750 instrument containing a 6 ft × 0.125 in. column packed with 10% UCW-98. [d] Obtained by desulfurization of the thiirane; yield based on thiirane. [e] Thiirane not isolated in pure form and desulfurization performed on crude thiirane; yield based on carbonyl compound. [f] Olefin not prepared. [g] Yield in parentheses based on recovered ketone. Thiirane decomposes at 125 °C. [h] Crude thiirane contained varying amounts of olefin (5–30%) and was taken directly to the olefin. [i] The NMR spectrum in benzene-d_6 was completely consistent with the exo structures shown. If the NMR spectrum is taken in deuteriochloroform, traces of HCl present in this solvent effects a slow isomerization to the endo (homoannular diene) compound. [j] Present as a mixture containing 85.5% trans and 14.5% cis isomers. [k] Present as a mixture containing 55% trans and 45% cis isomers.

Scheme IV

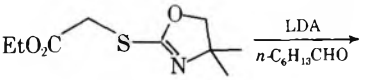


leaving group was confirmed by isolation of the oxazolidinone **19**. In many instances (Table I, entries 1–7, 13–16), the thiiranes were isolated as stable products. However, in those cases where the thiiranes contained an α-aryl or α-vinyl substituent (entries 8–11, 17–22), their thermal instability resulted in facile sulfur extrusion, producing thiiranes contaminated with varying amounts of diene or styryl systems. In this event, it was expeditious to by-pass the thiirane and transform the mixture directly to the olefinic product by heating with triphenylphosphine or triethyl phosphite. It is clear from the results in Table I that the alkylthio oxazolines are useful and efficient reagents for either the synthesis of thiiranes and/or the olefination of carbonyl compounds.

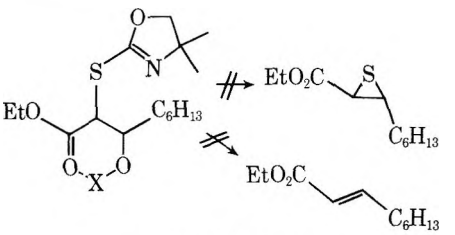
In order to assess the nature of this facile conversion of carbonyls to thiiranes, a study was performed to attempt isolation, by trapping, of the various intermediates **14**, **15**, and **16** in Scheme IV.

Oxazoline **6** (R = R′ = H) was metalated at −78 °C with *n*-butyllithium and treated with cyclohexanecarboxaldehyde. After 5 min and 1.5 h, while maintaining the temperature at −78 °C, the reaction was quenched with chlorotrimethylsilane and the only product isolated was the silyl ether **21**. Furthermore, if the initial adduct **14** was treated with chlorotrimethylsilane at −50, −25, and 0 °C the only product once again was **21** although traces (1–5%) of thiirane and **19** could be detected (TLC, NMR) from the 0 °C reaction. It is therefore concluded that the intramolecular addition of the lithium alkoxide to the C=N of the oxazoline (**14** → **15**) takes place mainly between 0 °C and room temperature. A number of attempts were made to trap the intermediate **16** prior to fragmentation but this process is apparently too rapid for interception.

Missing from Table I are thiiranes and olefins derived from 2-ethylthio- and 2-carboethoxymethylthiooxazolines **7** and **10**, respectively. In the former case, it was not possible to metalate the α-methylene group although a number of different bases and solvents were employed. It appears that the kinetic acidity of the α-methylene group is too low for proton removal unless there is present (except for CH_3S–) an activating group such as phenyl, vinyl, carbomethoxy, cyano, etc. This behavior has also been noted by others.[9,13] In the case of the carboethoxymethylthiooxazoline **10**, the α proton was readily removed by lithium diisopropylamide (−78 °C) and then treated with *n*-heptaldehyde. Workup after the reaction mixture reached room temperature gave no thiirane or evidence of the α,β-unsaturated ester, but only **22** (X = H) in 81%

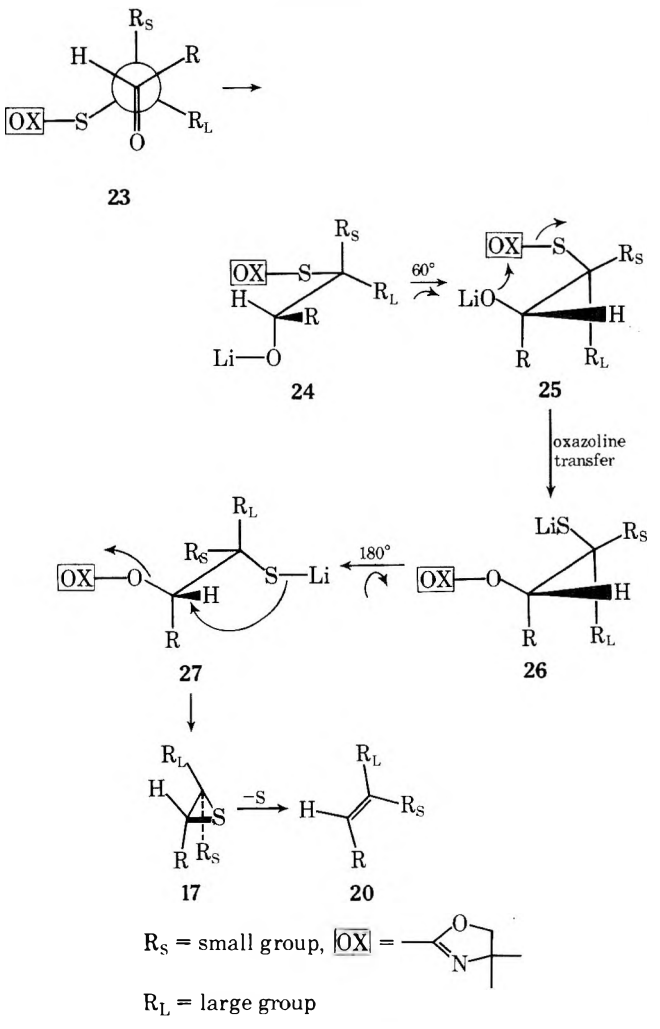


10



22 (X = Li, Na, H)

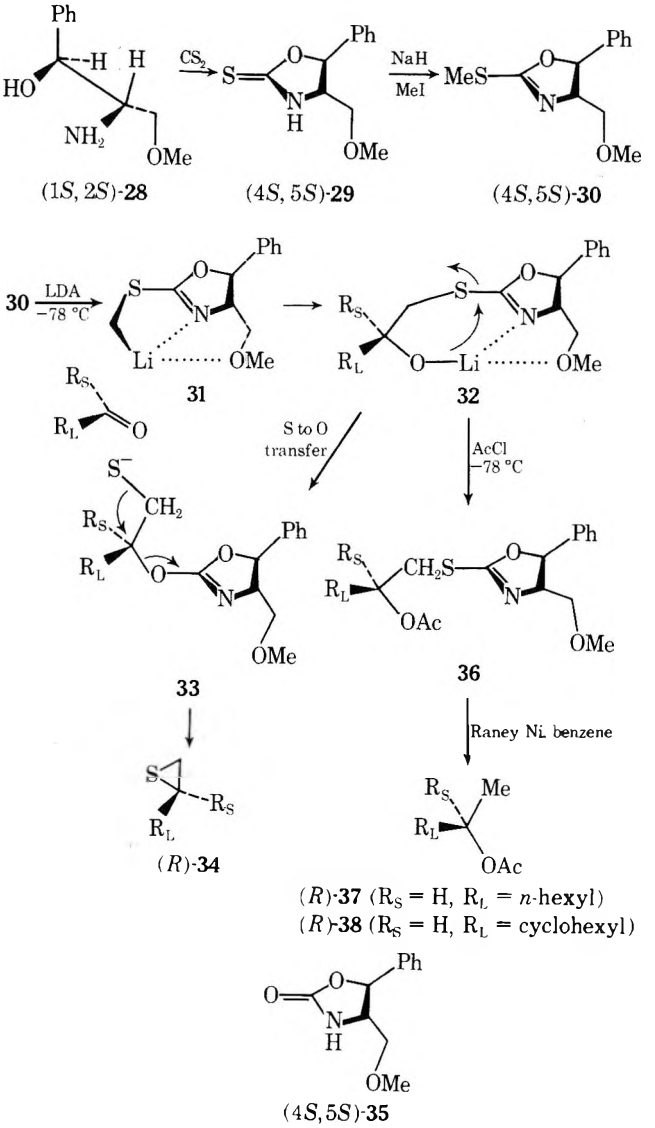
Scheme V



yield. Prolonged heating of the intermediate alkoxide (X = Li or Na) in THF or benzene at reflux returned mainly starting unreacted adduct **22** and some decomposition products. It is therefore apparent that the intermediate lithio adduct **22** is simply too stable in its chelated form to undergo rearrangement and fragmentation to the thiirane.

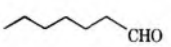
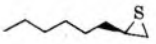
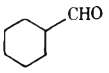
When 2-alkylthio-2-oxazolines **8**, **9**, and **11** are metalated and treated with carbonyl compounds, the resulting olefinic products were mixtures of *E*/*Z* isomers (Table I, entries 9, 15–17, 20–22). Except for 1-phenyl-1-octene (entry 16), which gave a 1.5:1 mixture of *E*/*Z* isomers, all the others were heavily in favor of the *E* isomer. This high degree of stereoselectivity can be readily understood by the formulations in Scheme V which show that carbonyl approach to the lithio thioalkyl oxazoline will occur to minimize nonbonded interactions (**23**). The resulting adduct **24** upon rotation to **25** now is properly aligned to allow S to O oxazoline transfer furnishing **26**. By 180° rotation the sulfide is now in a position to displace the oxazolidinone anion (**27**) producing the thiirane **17**. The latter is desulfurized via the stereospecific extrusion process[3b] providing the olefins **20**. That the olefin *E*, *Z* composition is, in fact, directly related to the geometric composition of the thiiranes was demonstrated in two instances. The thiiranes in entries 15 and 16 (Table I) were examined by NMR after purification by preparative layer chromatography. The NMR spectrum for 1,2-diphenylthiirane exhibited singlets at δ 7.37 (s, 10) and 3.97 (s, 2) for the trans isomer and δ 7.13 (s, 10) and 4.39 (s, 2) for the cis isomer in agreement with results previously obtained by Ketchum.[14] The integrated ratio for these signals indicated an 86:14 mixture of the trans to cis thiiranes. In a similar fashion, 1-phenyl-2-(*n*-hexyl)thiirane (entry 16, Table I) showed benzyl proton signals at δ 4.13 (q) and 3.58 (d) in a ratio of 55:45 suggesting that this thiirane had formed as an approximately equal mixture of isomers. Desulfurization of these thiiranes gave olefins in essentially the same isomeric ratio (Table I, entries 15, 16) thus confirming that the olefins produced in this study possess stereochemical compositions virtually identical with those for the thiirane precursors. The alkene and diene *E*, *Z* ratios reported in Table I were all determined by gas chromatography. Assignment of the *E* isomer in entry **20** as the major product was performed by ultraviolet spectroscopy since the compound had not been previously reported. The olefin exhibited an ultraviolet maxima at 217 and 247 nm as compared to 218 and 240 nm for the known (*E*)-2,3-diphenyl-2-butene.[15]

Chiral Thiiranes and Alkenes. Owing to the successful implementation of chiral oxazolines in asymmetric syntheses of various chiral carboxylic acids,[16] it was of interest to determine whether chiral thiiranes could be generated utilizing a chiral oxazoline. Toward this end, the chiral 2-thiomethyl oxazoline **30** was prepared starting from the methoxy amino alcohol **28**[16] and treatment with carbon disulfide which gave the thione **29**. Methylation of the latter using sodium hydride



furnished the desired chiral oxazoline. Treatment of **30** with lithium diisopropylamide gave the lithio salt **31** which on addition of various carbonyl compounds at −95 °C furnished, after aqueous quenching, the chiral thiiranes **34** in 48–70% yield and in enantiomeric purities of 19–32% (Table II). Since

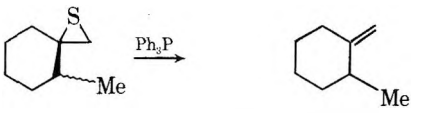
Table II. Chiral Thiiranes 34 from (4S,5S)-2-Thiomethyloxazolines

Entry	Carbonyl compd	Thiirane	Registry no.	% yield[a]	$[\alpha]_{589}^{25}$	% ee (confign)
1			58396-31-9	53	−3.45 (*c* 13.3, hexane)	21 (*R*)[c]
2			58396-32-0	67	−0.42 (*c* 7.1, hexane)	*d*
3			58396-33-1	64	+8.50 (*c* 14.5, PhH)	32 ± 6 (*R*)[c]
4	PhCHO		33877-15-5	48	−8.2 (*c* 2.2, heptane)	19 (*R*)[b]
5			58396-34-2	70	+4.95 (*c* 9.1, PhH)	(*R*)[c]

[a] Yields are of distilled or chromatographed products of >96% purity (VPC). [b] Based on literature value; see ref 17. [c] Configurations based on the corresponding acetates (see text). [d] Product was a diastereomeric mixture which was not separated but taken to the chiral olefin 39.

among the examples studied only phenylthiirane 34 (R_L = Ph; R_S = H) had been reported[17] and chiral shift reagents failed to provide enantiomeric compositions, an alternative route was investigated. As mentioned earlier, the rearrangement–fragmentation (32 to 33 to 34) occurs mainly above 0 °C and thus it appeared possible to trap 32 as its acetate 36. Reductive cleavage using Raney nickel furnished the chiral acetates 37 and 38. This scheme provided a measure of the asymmetric induction using the assumptions that (a) nucleophilic displacement by sulfide in 33 proceeds purely by inversion and (b) Raney nickel desulfurization of 36 affords the acetates 37 and 38 without racemization. If these conditions are met, then the acetates 37 and 38 possess enantiomeric purities and absolute configurations equal to that of the corresponding thiiranes 34 (R_L = *n*-hexyl, R_S = H; R_L = cyclohexyl, R_S = H). Thus, the chiral thiiranes in Table II (entries 1 and 3) are assigned the *R* configuration and their percent enantiomeric excess is based upon the known rotation for (*R*)-(−)-2-octyl acetate (37)[18] and the enantiomeric purity of 1-cyclohexyl-1-acetoxyethane (38). The latter was determined by use of a chiral shift reagent, Eu Optishift II, and its configuration has been previously assigned as *R*.[19]

The mechanism, as currently depicted for this asymmetric synthesis of thiiranes, indicates that the carbonyl group approaches the lithio alkylthio oxazoline 31 from the underside, such that the carbonyl oxygen may be complexed to the chelated lithium cation. The chelation as shown in 31 is in direct analogy with other chiral oxazolines which have been reported to alkylate in a similar manner.[16] In order to account for the configuration of the thiiranes, it is necessary to assume that the carbonyl group aligns itself under 31 in such a manner that the larger group (R_L) in the carbonyl component is as far away from the sulfur atom (*si* face) as possible since the reverse orientation (*ri* face) results in serious nonbonded interactions with the sulfur atom. This interaction is supported by examination of space filling models (Ealing). A similar orientation for carbonyl alkylation has already been discussed earlier with respect to the racemic thiiranes. If this mechanism is correct, then all the chiral thiiranes prepared in this study should be configurationally related, namely *R*. In a single instance, the chiral thiirane derived from 2-methylcyclohexane (Table II, entry 2) was heated with triphenylphosphine and provided a 69% yield of the chiral olefin 39. The enantiomeric purity was found to be 30 ± 5% as determined by adding silver trifluoroacetate to the sample which contained Eu Optishift II.[20] The absolute configuration of 39 is unknown.



39, $[\alpha]_{576}$ −0.45° (*c* 11, hexane)

Experimental Section

2-(Methylthio)-4,4-dimethyl-2-oxazoline (6). A solution of 26.2 g (200 mmol) of 4,4-dimethyloxazoline-2-thione (5)[12] in 250 ml of dry THF was added dropwise, with stirring (N_2) to 10.6 g (220 mmol) of 50% sodium hydride–mineral oil which had been previously washed with hexane (2 × 25 ml) to remove the mineral oil. Hydrogen evolution was complete after 2 h at room temperature. The resulting white suspension was then treated with 37.0 g (260 mmol) of methyl iodide in 20 ml of dry THF at ice bath temperature. The reaction mixture was warmed after 1 h at 0 °C to room temperature and partitioned between ether (100 ml) and saturated brine (150 ml). The aqueous phase was further extracted with ether (2 × 100 ml), the combined ethereal solutions were dried ($MgSO_4$) and concentrated, and the residue was distilled to give 25.0 g of a clear oil (86%), bp 82–84 °C (44 mm).[21]

2-(Ethylthio)-4,4-dimethyl-2-oxazoline (7). In a similar manner to that described above, using ethyl iodide, the product was formed in 85% yield: bp 132–134 °C (82 mm); ir (film) 1610 cm^{-1}; NMR ($CDCl_3$) δ 4.0 (s, 2), 2.97 (q, 2), 1.20–1.53 (s superimposed on t, 9).

Anal. Calcd for $C_7H_{13}NOS$: C, 52.83; H, 8.18. Found: C, 52.71; H, 8.11.

2-(Allylthio)-4,4-dimethyl-2-oxazoline (8) was prepared from allyl bromide, 5, and sodium hydride furnishing 16.1 g (94%) of 8: bp 55 °C (0.25 mm); ir (film) 1610, 1640, 3080 cm^{-1}; NMR ($CDCl_3$) δ 5.67–6.30 (m, 1), 5.00–5.46 (m, 2), 4.00 (s, 2), 3.65 (d, 2, *J* = 6 Hz), 1.31 (s, 6).

Anal. Calcd for $C_8H_{13}NOS$: C, 56.10; H, 7.65. Found: C, 56.10; H, 7.77.

2-(Benzylthio)-4,4-dimethyl-2-oxazoline (9) was prepared from 2.0 equiv of benzyl chloride and 5: 79% yield; bp 123 °C (0.3 mm); ir (film) 1610, 3015, 1500, 1440 cm^{-1}; NMR ($CDCl_3$) δ 7.33 (s, 5), 4.26 (s, 2), 4.02 (s, 2), 1.32 (s, 6).

Anal. Calcd for $C_{12}H_{15}NOS$: C, 65.12; H, 6.83. Found: C, 65.37, H, 6.99.

2-(Carboethoxymethylthio)-4,4-dimethyl-2-oxazoline (10) was prepared from ethyl α-bromoacetate, 5, and sodium hydride: 56% yield; bp 79–81 °C (0.1 mm); ir (film) 1610, 1740 cm^{-1}; NMR ($CDCl_3$) δ 4.21 (q, 2), 4.04 (s, 2), 3.80 (s, 2), 1.25 (t, 9).

Anal. Calcd for $C_9H_{15}NO_3S$: C, 49.77; H, 6.91. Found: C, 49.88; H, 6.88.

2-(α-Phenethylthio)-4,4-dimethyl-2-oxazoline (11). A solution of 5.5 g (25 mmol) of 2-(benzylthio)-4,4-dimethyloxazoline (9) in 175 ml of dry THF was cooled (N_2) to −78 °C and treated with 11.5 ml of 2.3 M *n*-butyllithium in hexane (26.5 mmol). The resulting red-orange solution was stirred for 2 h at −78 °C and treated with 3.90 g (27 mmol) of methyl iodide. The reaction mixture was slowly allowed to

Table III. Physical Data for Thiiranes 17

Registry no.	Thiirane entry (from Table I)	NMR ($CDCl_3$), δ	Mp, °C
58437-20-0	1	2.70–3.17 (m, 1), 2.50 (d, 1, J = 6 Hz), 2.17 (d, 1, J = 6 Hz), 0.6–2.00 (m, 13)	*a*
58437-21-1	2	2.52–2.97 (m, 1), 2.50 (d, 1, J = 6 Hz), 2.20 (d, 1, J = 6 Hz), 0.73–2.13 (m, 11)	*b*
58462-45-6	3	4.30–4.66 (m, 9), 3.30–4.30 (m, 3)	>200 dec
58437-22-2	4	2.36–2.46 (m, 2), 1.00–2.10 (m, 8) 1.50 (s, 3)	*c*
58396-35-3	5	2.43 (s, 2), 1.16–2.40 (m, 14)	*b*
58396-36-4	6	7.26 (s, 5), 3.03 (q, AB, J = 2, 14 Hz, 2) (d, J = 6 Hz, 2), 1.50 (s, 3)	*c*
58396-37-5	7	2.34 (br d, J = 8 Hz, 2), 0.80–2.40 (m, 16)	*b*
	13	2.35 (br d, J = 5 Hz, 2), 1.15–2.20 (m, 9), 1.01 (d, J = 7 Hz, 3)	*b*
58396-38-6	14	5.23–5.46 (m, 1), 4.60–4.86 (m, 1), 3.20–4.17 (m, 2), 0.6–2.80 (m, 33) includes Me at 0.90 (s, 3), 1.00 (s, 3), 2.46 (br d, J = 8 Hz, 2)	138–140[c]
57694-36-7	15	trans 7.37 (s, 10), 3.97 (s, 2)	52–54[d]
3372-81-4		cis 7.13 (s, 10), 4.39 (s, 2)	
58396-39-7	16	7.30–7.35 (br s, 5), 4.13 (q, 0.5), 3.58 (d, J = 5 Hz, 0.5)	*b*

[a] C. G. Moore and M. Porter, *J. Chem. Soc.*, 2062 (1958). [b] Since these thiiranes were transformed into olefins, the latter were characterized (cf. Table IV). [c] Analysis performed and gave ±0.4% of calculated values. [d] R. Ketchum and V. P. Shah, *J. Org. Chem.*, 28, 229 (1963).

Table IV. Trimethylsilyl Chloride Trapping of Alkoxide 14. Formation of 21

Temp of aliquot,[a] °C	TLC, R_f (benzene)	Ir, cm^{-1} (film)	NMR ($CDCl_3$), δ	Products
−78 (5 min)	0.55	1610	4.00 (s, 2), 3.50–3.87 (m, 1), 3.00–3.20 (dd, 2), 0.66–2.00 (m, 17), 0.13 (s, 9)	21
−78 (90 min)	0.55	1610	4.00 (s, 2), 3.50–3.87 (m, 1), 3.00–3.20 (dd, 2), 0.66–2.00 (m, 17), 0.13 (s, 9)	21
−50 (90 min)	0.55	1610	4.00 (s, 2), 3.50–3.87 (m, 1), 3.00–3.20 (dd, 2), 0.66–2.00 (m, 17), 0.13 (s, 9)	21
−25 (90 min)	0.55	1610	4.00 (s, 2), 3.50–3.87 (m, 1), 3.00–3.20 (dd, 2), 0.66–2.00 (m, 17), 0.13 (s, 9)	21
0 (90 min)	0.55, 0.90 (faint)	1610	Same as above plus small peak at 0.37	21 + 19[b]
25 (30 min)	0.9, 0.15, 0.55 (faint)	1740 (s) 1610 (w)	Weak signals for 21, 3.93 (s), 1.37 (s), 0.37 (s), 2.20 (d, J = 6 Hz), 2.50 (d, J = 6 Hz), 2.52–2.97 (m)	17,[c] 19[b]

[a] Elapsed time after addition of cyclohexanecarboxaldehyde in parentheses. [b] Product is 19 as its *N*-trimethylsilyl ether. [c] Product is 2-cyclohexylthiirane.

warm to room temperature (~3 h) and the reaction mixture partitioned between ether and saturated brine. The aqueous layer was extracted once with ether and the combined ethereal extracts were dried ($MgSO_4$) and concentrated. Distillation gave 5.2 g (89%) of pure material (by VPC): bp 116–117 °C (0.1 mm); ir (film) 3030, 1605 cm^{-1}; NMR ($CDCl_3$) δ 7.33 (s, 5), 4.78 (q, 1), 3.95 (s, 2), 1.75 (d, 3), 1.3 (s, 6). Product was homogeneous by VPC.

Anal. Calcd for $C_{13}H_{17}NOS$: C, 66.34; H, 7.28. Found: C, 66.26; H, 7.39.

Ethyl α-(4,4-Dimethyloxazolinethio)propionate (12). A solution of 2.17 g (10 mmol) **10** in 50 ml of dry THF was cooled to −78 °C (N_2) and treated with lithium diisopropylamide (10 mmol in 10 ml of dry THF). Stirring was continued for 3 h, 0.7 ml (1.56 g, 11 mmol) of methyl iodide added, and the solution allowed to warm to room temperature. Aqueous quenching followed by ether extraction and concentration gave 1.9 g (82%): bp 83.5 °C (0.06 mm); ir (film) 1610, 1735 cm^{-1}; NMR ($CDCl_3$) δ 4.35–4.06 (m, 3), 4.06 (s, 2), 1.63 (d, 3), 1.13–1.50 (s superimposed on t, 9). Product was homogeneous by VPC.

Anal. Calcd for $C_{10}H_{17}NO_3S$: C, 51.95; H, 7.36. Found: C, 51.99; H, 7.28.

The formation of **12** was also achieved by utilizing the sodium salt of **5** (100 mmol) and 16.2 g (100 mmol) of ethyl α-bromopropionate according to the procedure given for **6**. This provided 20.0 g of **12**, homogeneous by VPC, in 82% yield.

General Procedure for Thiiranes (17). Method A (Table I). A solution of 10 mmol of 2-(alkylthio)-4,4-dimethyl-2-oxazolines **6**, **8**, **9**, and **11** in 50 ml of dry THF (0.2 M) under nitrogen at −78 °C was treated with 10 mmol of *n*-butyllithium (hexane). After 2 h at −78 °C, 10 mmol of the carbonyl compound was introduced dropwise via syringe either neat (if liquid) or in 10 ml of THF if solid and the reaction mixture stirred for 30 min at −78 °C. After warming to room temperature (1–2 h) the reaction mixture was quenched in saturated brine (100 ml) and extracted with 50 ml of ether (twice). The ethereal extracts were dried ($MgSO_4$) and concentrated to give the crude thiiranes along with the oxazolidinone **19**. Chromatography (benzene, silica gel) gave the pure thiiranes (TLC R_f 0.85–0.95) listed in Table I. Further elution of the silica gel column (benzene–ether, 5:1) provided pure **19**, mp 55–56 °C (lit.[22] 55.6–56.4 °C). Physical data and literature references for the thiiranes prepared in this manner are given in Table III.

Alkoxide-Trapped Trimethylsilyl Ether 21. A solution of 2-(methylthio)-4,4-dimethyloxazoline (**6**, 1.45 g, 10 mmol) in 30 ml of dry THF was cooled to −78 °C (N_2) and treated with 4.5 ml of 2.3 M *n*-butyllithium in hexane. After 2.5 h at −78 °C, a solution of 1.12 g (10 mmol) of cyclohexanecarboxaldehyde in 5 ml of THF was added via a syringe. After 5 and 90 min, aliquots were removed (8 ml) and quenched in 5 ml of THF containing 0.3 ml (1.1 equiv) of trimethylchlorosilane. Similarly, aliquots were taken at −50, −25, 0, and 25 °C and quenched in the trimethylchlorosilane–THF solution. In all cases, the quenching solution was at the same temperature as the aliquot removed from the reaction mixture. Workup of each aliquot by ether extraction, drying, and concentration gave the results summarized in Table IV.

General Procedure for Conversion of Carbonyl Compounds Directly to Alkenes 20. Method B (Table I). The general procedure for alkylation of the lithio alkylthio oxazolines with carbonyl compounds was followed as for thiiranes **17** up to the purification stage using column chromatography. Instead of column purification, the crude thiirane **17** contaminated with the oxazolidinone **19** was treated either with 1.15 equiv of neat triphenylphosphine at 90 °C for 2 h or with 1.5 equiv of triethyl phosphite at 90 °C for 2 h. When triphenyl phosphine was used, the reaction mixture was allowed to cool, the reflux condenser was replaced by a short path distillation head, and the olefinic products were distilled. When triethyl phosphite was used

Table V. Physical Data for Olefins 20

Registry no.	Olefin entry (from Table I)	Desulfurization reagents	Ir, cm^{-1} (film)	NMR ($CDCl_3$), δ	Lit. bp, °C
111-66-0	1	Ph_3P	1640, 3078		118–120[a]
695-12-5	2	Ph_3P	1638, 3080		125–127[b]
3618-18-6	5	Ph_3P	1635, 3080	4.80 (br s, 2), 1.30–2.26 (m, 14)	154–156[c]
58396-40-0	7	Ph_3P	1650, 3080	4.46–4.70 (br s, 2), 0.70–2.40 (m, 16)	200–201[d]
13511-13-2	8	Ph_3P	1600, 1660, 3080	5.90 (m, 1), 4.93 (br d, 2), 1.90 (s, 3), 1.50–2.50 (m, 11)	49–50 (7 mm)[e]
16939-57-4	9	$(EtO)_3P$	1610, 1640	7.03–7.53 (m, 5), 6.10–6.80 (m, 3), 5.00–5.43 (m, 2)	86 (11 mm)[e,f]
25108-63-8	10	$(EtO)_3P$	1635, 3080	7.53–7.83 (m, 1), 7.03–7.46 (m, 3), 5.50 (br s, 1), 4.96 (br s, 1), 1.60–3.00 (m, 6)[g]	103 (14 mm)[h]
57662-71-2	11	$(EtO)_3P$	1610, 1650, 3080	7.00–7.50 (m, 4), 6.03 (br s, 1), 4.77 (br s, 2), 1.47 (s, 3), 1.13–3.10 (m, 11)[g]	Oil[i]
627-58-7	12	Ph_3P	1645, 3080	4.70 (br s, 4), 2.17 (s, 4), 1.73 (t, J = 2 Hz, 6)	110–112[j]
58396-41-1	13	Ph_3P	1642, 3075	4.60 (br s, 2), 0.77–2.57 (m, 12)	145[k]
103-30-0 645-49-8	15	$(EtO)_3P$	*E, Z* mixture		113–116[n]
28665-60-3 42036-72-6	16	$(EtO)_3P$	*E, Z* mixture		144 (10 mm)[l]
538-81-8 5808-05-9	17	$(EtO)_3P$	*E, Z* mixture		(mp 141–144)[m]
58396-42-2	18	$(EtO)_3P$	1600, 1575	7.26 (m, 5), 6.30 (br s, 1), 2.06–2.60 (m, 4), 1.3–2.00 (m, 10)	Oil[o]
3677-70-1	19	$(EtO)_3P$	1600, 3020	7.33 (s, 5), 7.16 (s, 5), 6.97 (br s, 5), 2.16 (s, 3)	Oil
58396-43-3	20	$(EtO)_3P$	1600, 3020	*E, Z* mixture	Oil[p]
58396-44-4	21	$(EtO)_3P$	Identical with entry 9		
58396-45-5	22	$(EtO)_3P$	1650, 1600, 3090, 1010	4.85–6.70 (m, 4), 1.80–2.46 (m, 2), 0.50–1.80 (m, 11)	168–170[q]

[a] Huntress and Mulliken, "Identification of Pure Organic Compounds", Order 1, Wiley, New York, N.Y., 1941, p 586. [b] L. F. Slaugh and E. F. Magoon, *J. Org. Chem.*, 27, 1037 (1962). [c] W. T. Brady and A. D. Patel, *Synthesis*, 565 (1972). [d] M. Mousseron and R. Granger, *C. R. Acad. Sci.*, 217, 483 (1943), mixture of cis–trans isomers. [e] P. S. Wharton and B. T. Au, *J. Org. Chem.*, 31, 3787 (1966). [f] O. Grummitt and E. I. Becker, *J. Am. Chem. Soc.*, 70, 149 (1948). [g] Spectrum taken in CCl_4 or benzene-d_6; see footnote *i*, Table I. [h] G. Schroeder, *Ber.*, 58B, 713 (1925). [i] Pure sample from silica gel chromatography (benzene). Anal. Calcd for $C_{16}H_{18}$: C, 91.40; H, 8.57. Found: C, 91.19; H, 8.40. [j] E. Muller and G. Roscheisen, *Ber.*, 90, 543 (1957). [k] B. Bailey, R. D. Haworth, and J. McKenna, *J. Chem. Soc.*, 967 (1954). [l] R. Y. Mixer and W. G. Young, *J. Am. Chem. Soc.*, 78, 3379 (1956). [m] B. B. Corson, "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943, p 229; mp for pure trans,trans is 152.5–153.5 °C. [n] W. Schlenk and E. Bergman, *Justus Liebigs Ann. Chem.*, 463, 98 (128). [o] Pure sample from silica gel (benzene). Anal. Calcd for $C_{15}H_{20}$: C, 90.00; H, 10.00. Found: C, 89.89; H, 9.78. [p] Pure sample from silica gel (benzene). Anal. Calcd for $C_{21}H_{24}$: C, 91.25; H, 8.75. Found: C, 90.96; H, 8.80. [q] H. Fournier, *Bull. Soc. Chim. Fr.*, 13, 884 (1918).

as the desulfurization agent, the mixture was applied to a column (silica gel) and eluted with benzene. Physical data for the olefins prepared are presented in Table V.

(1*S*,2*S*)-(+)-1-Phenyl-2-amino-3-methoxy-1-propanol (28). To a solution of 20.5 g (100 mmol) of (4*S*,5*S*)-2-methyl-4-methoxymethyl-5-phenyl-2-oxazoline[16,23] in 400 ml of ethanol was added 100 ml of 12 M aqueous hydrochloric acid (1.2 mol, 12-fold excess). The resulting solution was heated under reflux for 8 h, cooled to room temperature, and the ethanol removed under reduced pressure. Slow, cautious addition to the aqueous residue (ice bath) of KOH pellets and ether extraction provided 17.3 g after removal of the ether. Crystallization from ether (−78 °C) gave 15.5 g (86%) of **28**, mp 48–50 °C, $[\alpha]_{589}^{25}$ +25.8° (*c* 8.55, $CHCl_3$) [lit.[16] mp 48–50 °C, $[\alpha]_{589}^{25}$ +24.4° (*c* 10.6, $CHCl_3$)].

(4*S*,5*S*)-(−)-4-Methoxy-5-phenyl-2-oxazolidine-2-thione (29). To a solution of 18.1 g (100 mmol) of (+)-**28** in 250 ml of dry DMF at ice bath temperature was added 6.4 ml (107 mmol) of carbon disulfide, and the resulting yellow-orange solution stirred (0 °C) for 1 h. The solution was heated in an oil bath (80 °C, 2 h), cooled to room temperature, and the residual hydrogen sulfide removed in vacuo in a hood overnight. The DMF was evaporated in vacuo and the residue partitioned between ether and saturated brine. The ether layer was washed with 1 M sodium bicarbonate, followed by 1 M HCl, and finally with water, dried ($MgSO_4$), and concentrated. The residue was recrystallized from carbon tetrachloride yielding 15 g (67%) of **29**: mp 88–89 °C; $[\alpha]_{589}^{25}$ −14.4° (*c* 6.05, $CHCl_3$); ir ($CHCl_3$) 3400, 3200, 1550–1460 cm^{-1}; NMR ($CDCl_3$) δ 8.17 (br s, 1), 7.43 (s, 5), 5.72 (d, J = 6 Hz, 1), 3.93–4.30 (m, 1), 3.43–3.73 (m, 5). Elemental analyses performed on the 2-thiomethyl derivative **30** given below.

(4*S*,5*S*)-(−)-2-Methylthio-4-methoxymethyl-5-phenyloxazoline (30). A solution of 11.15 g (50 mmol) of (−)-**29** in 125 ml of dry THF was added dropwise (N_2) to 2.7 g (55 mmol) of a 50% sodium hydride suspension (previously washed twice with 20-ml portions of hexane). Gas evolution was complete after 1.5 h. The resulting mixture was treated with 9.3 g (65 mmol) of methyl iodide in 15 ml of dry THF at 0 °C and after 1 h allowed to warm to 25 °C. The mixture was partitioned between ether (100 ml) and saturated brine (150 ml). The aqueous phase was extracted (2 × 75 ml) and the ethereal solutions combined, dried ($MgSO_4$), and concentrated. The residue was distilled, bp 140–142 °C (0.25 mm), to give 9.1 g (80%) of **30**: $[\alpha]_{589}^{25}$ −42.4° (*c* 10.3, $CHCl_3$); ir (film) 1610 cm^{-1}; NMR ($CDCl_3$) δ 7.35 (s, 5), 5.45 (d, J = 6 Hz, 1), 3.97–4.33 (m, 1), 3.33–3.80 (m, 2), 3.43 (s, 3), 2.53 (s, 3).

Anal. Calcd for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.73. Found: C, 60.82; H, 6.55.

General Procedure for Chiral Thiiranes 34. A solution of 1.2 g (5 mmol) of **30** in 25 ml of dry THF (0.25 M) was cooled to −78 °C (N_2) and treated with 1.05 equiv of lithium diisopropylamide. After 4 h at −78 °C, the mixture was cooled to −95 °C and the carbonyl compound (1.0 equiv) was added dropwise in 5 ml of THF. The reaction was maintained at −95 °C for 1 h and then allowed to warm to 25 °C. The mixture was quenched in saturated brine solution and extracted several times with ether, then dried ($MgSO_4$) and concentrated. The pure thiiranes were obtained by passing through a silica gel column using benzene as the eluent. Further elution using ether gave the chiral oxazolidinone **35**: ir 3300, 1760 cm^{-1}; NMR ($CDCl_3$) δ 7.37 (s, 5), 5.3 (d, J = 6 Hz, 1), 4.10–3.73 (q, 1), 3.63–3.40 (m, 2), 3.40 (s, 3).

The chiral thiiranes prepared in this manner are presented in Table II. No spectral data are presented for **34** since they were found to be identical with their racemic counterparts (**17**) given in Table III.

Alkoxide Trapped Acetates 36. General Procedure. The procedure above (for **34**) was followed up to the reaction of the carbonyl compound with the lithio thiomethyloxazoline **31** at −95 °C for 1 h. At the end of this period, the mixture was warmed to −78 °C for 2 h and then treated with 0.37 g (5.25 mmol) of freshly distilled acetyl chloride. After a further 2 h at −78 °C, the reaction mixture was allowed to warm slowly to 25 °C and quenched in saturated brine solution. Ether extraction followed by drying ($MgSO_4$) and concentration gave the acetates **36** (85–95% purity via NMR). The major impurity was 5–10% of starting oxazoline **30**. Physical data for **36** follow.

36 (R_S = H; R_L = *n*-hexyl): 76% yield; ir (film) 1750, 1610 cm^{-1}; NMR ($CDCl_3$) δ 7.37 (s, 5), 5.45 (d, J = 6 Hz, 1), 2.93–4.37 (m, 9), 2.07 (s, 3), 0.67–1.93 (m, 13).

36 (R_S = H; R_L = cyclohexyl): 75% yield; ir (film) 1740, 1610 cm^{-1}; NMR ($CDCl_3$) δ 7.37 (s, 5), 5.30–5.60 (m, 1), 3.03–4.43 (m, 9), 0.67–2.26 (m, 11).

These materials were not purified further and were used as obtained for the desulfurization to **37**.

Chiral Acetates 37 and 38. The Raney nickel reagent for the desulfurization was prepared by removal of the ethanol from a tenfold weight excess of W-4 Raney nickel as the benzene–ethanol azeotrope. Sufficient benzene was included so that the volume of solvent present after removal of the azeotrope was approximately 50 ml. A solution of the acetates **36** (4 mmol in 10 ml of dry benzene) was added to the suspension and the resulting mixture heated for 3 h at reflux. Cooling, filtration, and fractional distillation of the benzene gave the crude acetates **37**. Pure samples were obtained by preparative gas chromatography. Physical data follow.

37 (R_S = H; R_L = *n*-hexyl): $[\alpha]_{589}^{25}$ −1.36° (c 2.21, EtOH), reported[18] $[\alpha]_{589}^{25}$ −6.5° (c 5, EtOH); absolute configuration designated as *R*.

38 (R_S = H; R_L = cyclohexyl): $[\alpha]_{589}^{25}$ −1.6° (c 1.1, CCl_4); optical purity determined by Eu Optishift II [tris(heptafluoropropylhydroxymethylene-*d*-camphorato)europium(III)]. Absolute configuration of the (−) alcohol and (−) acetate is known.[19]

(−)-Methylene(2-methyl)cyclohexane (39). A mixture of 586 mg (4 mmol) of the chiral thiirane **34** (Table II, entry 2) and 1.2 g (4.6 mmol) of triphenylphosphine was heated to 90 °C for 2 h. The mixture was cooled to room temperature and the reflux condenser replaced with a short-path distillation head. Distillation gave 303 mg (69%) of **39**. The observed optical rotation at 589 nm was <0.01° and thus too low to permit a reliable $[\alpha]$ value; these rotations were, therefore, taken (Jasco DIP-180 automatic polarimeter) at 576 nm, which gave an observed rotation of −0.05° or $[\alpha]_{576}^{25}$ −0.45° (*c* 11, hexane). The spectral characteristics (ir, NMR) were identical with those of the racemic compound (entry 13, Tables I, V). The enantiomeric purity of **39** was determined as follows, which represents a modification of the method of Evans.[20]

A solution of 29 mg (0.26 mmol) of **39** was dissolved in 0.66 ml of CCl_4, containing 1% Me_4Si, to give approximately a 0.4 M solution. Addition of 0.13 mmol of both silver trifluoroacetate and Eu Optishift II [in place of Eu([$^2H_9$]fod)$_3$ used in the reported[20] procedure] was followed by shaking the solution until all the solid had dissolved. Examination of the 60-MHz spectrum gave partial resolution of the terminal vinyl protons. Integration and peak height comparison indicated that the enantiomeric purity was 30 ± 5%.

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Registry No.—**5**, 54013-55-7; **6**, 53244-68-1; **7**, 58396-17-1; **8**, 58396-18-2; **9**, 53244-69-2; **10**, 58396-19-3; **11**, 58396-20-6; **12**, 58396-21-7; **21**, 58396-22-8; **28**, 51594-34-4; **29**, 58396-23-9; **30**, 58396-24-0; **31**, 58396-25-1 **35**, 58396-26-2; **36** (R_S = H; R_L = hexyl), 58396-27-3; **36** (R_S = H; R_L = cyclohexyl), 58396-28-4; **37**, 54712-18-4; **38**, 58396-29-5; **39**, 58396-30-8; methyl iodide, 74-88-4; ethyl iodide, 75-03-6; allyl bromide, 106-95-6; benzyl chloride, 100-44-7; ethyl α-bromoacetate, 105-36-2; (4*S*,5*S*)-2-methyl-4-methoxymethyl-5-phenyl-2-oxazoline, 52075-14-6.

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Reaction of 2-Amino-7-chloro-5-phenyl-3*H*-[1,4]benzodiazepine with 1,3-Dicarbonyl Compounds[1]

Jacob Szmuszkovicz,* Lubomir Baczynskyj, Constance C. Chidester, and David J. Duchamp

Research Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001

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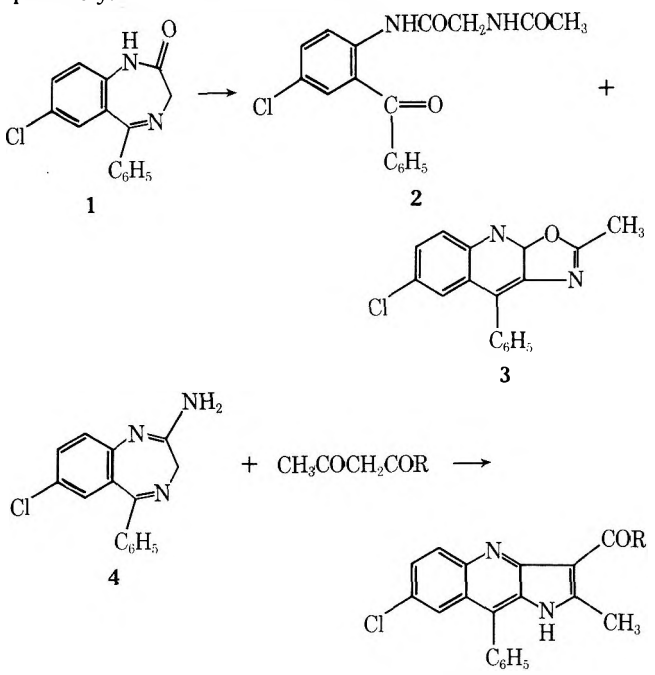
An interesting rearrangement was observed in the reaction of 2-amino-7-chloro-5-phenyl-3*H*-[1,4]benzodiazepines with 1,3-carbonyl compounds. On the basis of spectral data and chemical properties, the structures of the reaction products were assigned as possessing a rearranged ring system of 1*H*-pyrrolo[3,2-*b*]quinoline. The structure of one of these, namely the 1-[3-(dimethylamino)propyl] derivative of compound **5**, was confirmed by x-ray analysis.

A number of diverse rearrangements have been observed in the 1,4-benzodiazepine class of compounds.[2] One of these involved the transformation of compound **1** to anilide **2** and quinoline **3** when **1** was heated with acetic anhydride in the presence of either sulfuric acid or sodium acetate.[3]

We have now observed another example of the quinoline-type rearrangement. Thus, the reaction of 2-amino-7-chloro-5-phenyl-3*H*-[1,4]benzodiazepine (**4**) with ethyl acetoacetate, *tert*-butyl acetoacetate, and acetylacetone produced the 1*H*-pyrrolo[3,2-*b*]quinoline derivatives **5**, **6**, and **7** respectively.



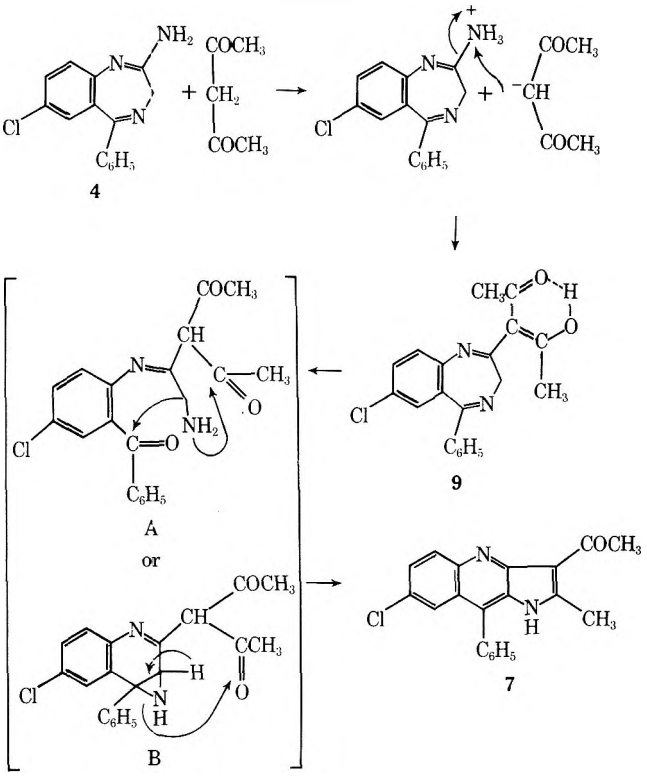
1 **2** **3** **4**

5, R = OEt
6, R = O-*t*-Bu
7, R = Me
8, R = OH

The proposed mechanism of this transformation in the case of the reaction of **4** with acetylacetone is shown in Scheme I. Initial displacement of the NH_2 group by an acetylacetone anion gave rise to compound **9**, which was isolated (as the enol) along with **7**. Compound **9** is visualized as rearranging to **7** either via the open-chain amino ketone A or via the aziridine B.

The structures of the rearrangement products **5**, **6**, and **7** are supported by spectroscopic data (see Experimental Section). For example, compound **6** showed a broad NH absorption at 2900 cm^{-1} and C=O at 1685 cm^{-1} in the infrared; extended conjugation in uv; C–CH_3 at δ 2.83, *tert*-butyl at δ 1.81, and no CH_2 or CH in the NMR; the mass spectrum gave a peak at *m/e* 41 (CH_3CN) indicative of N–C–CH_3 moiety. The ultraviolet spectra of **5**, **6**, and **7** were similar which indicated

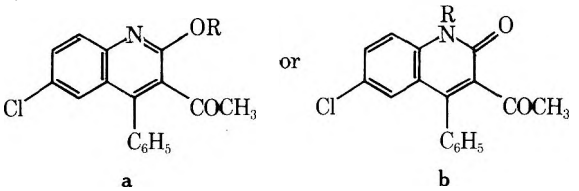
Scheme I



that these compounds possess the same chromophore and belong to the same structural class.

Treatment of **6** with trifluoroacetic acid gave the corresponding acid **8**.

From the reaction of **4** with *tert*-butyl acetoacetate a by-product was isolated and identified as **10** (**a** or **b**) by independent synthesis from 2-amino-5-chlorobenzophenone with either ethyl acetoacetate or *tert*-butyl acetoacetate. Compound **10** was alkylated with 2-dimethylaminoethyl chloride to give a compound which possesses either structure **11a** or **11b**.

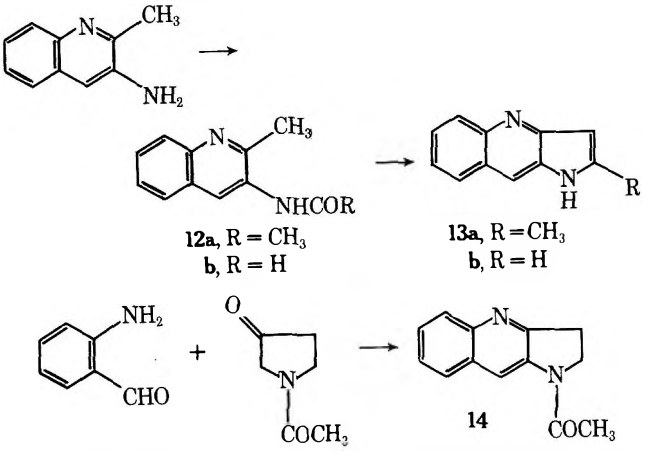


a **b**

10, R = H
11, R = $CH_2CH_2N(CH_3)_2$

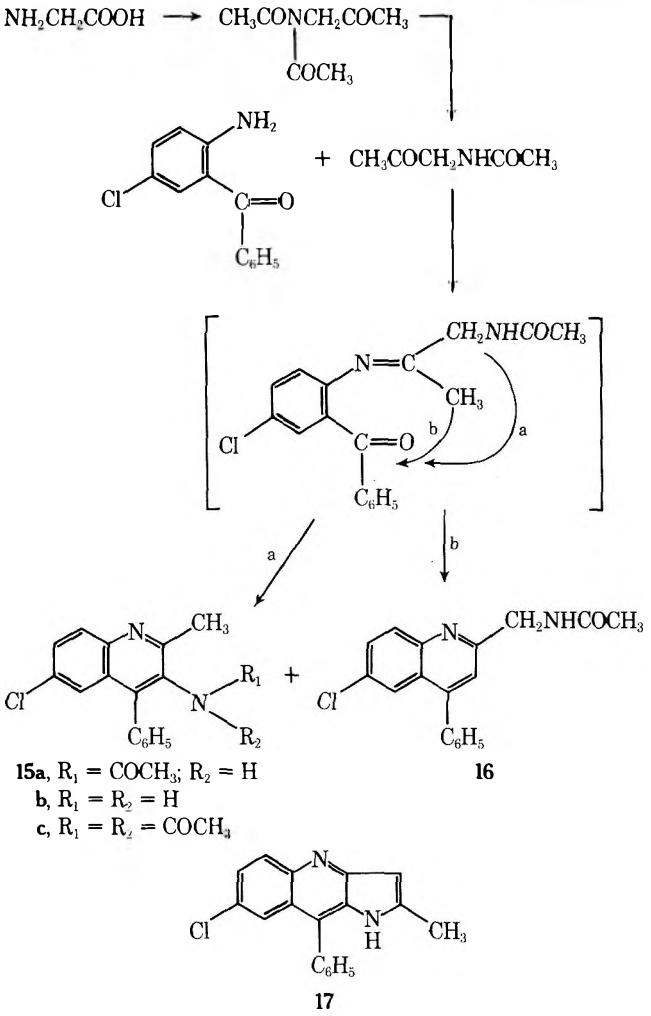
The compounds described above appear to be the first examples of the 9-phenyl substituted-1*H*-pyrrolo[3,2-*b*]quinoline ring system. The corresponding dephenyl ring system (**13a,b**) was prepared earlier from 3-amino-2-methylquinoline by the Madelung reaction either via the 3-acetylamino (**12a**)[4]

or the 3-formylamino (**12b**)[5] derivatives. The analogous 2,3-dihydro ring system (**14**) had been prepared from *N*-acetyl-3-pyrrolidone and *o*-aminobenzaldehyde by the base-catalyzed Friedländer condensation.[6]



Our attempts to synthesize 7-chloro-2-methyl-9-phenyl-1*H*-pyrrolo[3,2-*b*]quinoline (**17**) for eventual comparison with the rearrangement products were terminated when it was found that the 1-[3-(dimethylamino)propyl] derivative of compound **5**, which formed triclinic crystals, was amenable to x-ray determination. Compounds **5** and **7** formed tetragonal crystals. Computer programs for determining their crystal structure were not readily available in our laboratory.

The attempts to synthesize **17** involved *N*-acetonylacetamide as a synthon for the construction of the suitably substituted quinoline ring system for a subsequent Madelung reaction. Thus, condensation of 2-amino-5-chlorobenzophenone with *N*-acetonylacetamide,[7] prepared from glycine in two steps, afforded a mixture of **15a** and **16**, easily separable by chromatography.



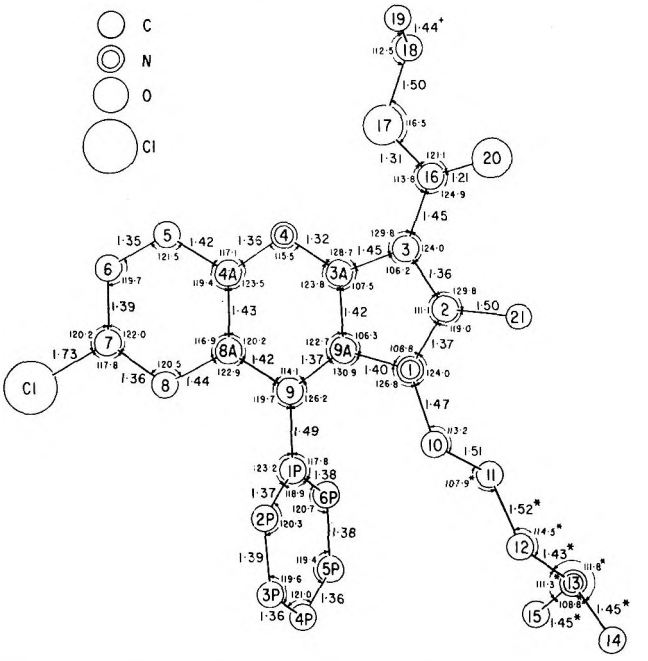


Figure 1. Mean bond distances (Å) and angles (degrees) for the two molecules. Standard deviations for distances are about 0.01 Å, for angles, about 0.5°. * Value obtained for unprimed molecule; + Corrected for thermal motion using "riding motion" mode.[13a]

Attempted reaction of **15** with sodamide in refluxing *N,N*-diethylaniline gave the deacetylated product, 3-amino-6-chloro-2-methyl-4-phenylquinoline (**15b**). The treatment of the *N,N*-diacetyl derivative **15c** with sodium ethoxide at 285 °C,[8] or treatment of **15a** with phosphorus oxychloride, followed by first dimethylacetamide and then potassium hydroxide,[9] also failed to yield **17**. A trace of the desired compound (**17**, M^+ *m/e* 292) along with its monochloro derivative (M^+ *m/e* 326) was found in the mass spectrum of the mixture obtained from the reaction of **15a** with phosphorus pentachloride in chloroform followed by treatment with triethylamine. A trace of the molecular ion M^+ *m/e* 292 was observed also from the products of the treatment of **15a** with potassium *tert*-butoxide at 255–270 °C.

In the course of these attempts the 1-*N*-oxide of **15a** was prepared but was not subjected to further experimentation.

Discussion of X-Ray Results. The structure of the 1-[3-(dimethylamino)propyl] derivative of **5** was determined by single-crystal x-ray analysis using direct methods. Final atomic coordinates are given in Table I. There are two symmetry-independent molecules which are very similar in conformation. The only difference worthy of note between the two is that the NMe_2 group in the molecule with primed numbers is probably disordered (see Experimental Section), as evidenced by exceptionally high anisotropic temperature factors.[10] Figure 1, which is drawn from x-ray coordinates, shows mean distances and angles. Hydrogens are not shown. The fused ring portion of the molecule is flat; the largest deviations from the least-squares planes calculated for the fused rings are 0.06 and 0.04 Å for C9 and C9′. The plane of the phenyl ring is approximately perpendicular (85 and 88°) to the plane of the fused rings. The carboxyl group is twisted about 10° out of the plane of the fused rings. The pattern of long and short bond lengths in the quinoline portion of the molecule is consistent with values reported in the literature for quinoline and acridine ring systems,[11,12] and can be explained by resonance structures.

Table I. Final Atomic Coordinates (× 10^4) for the 1-[3-(Dimethylamino)propyl] Derivative of 5. Standard Deviations are in Parentheses

	X	Y	Z
CL	7997 (2)	6174 (2)	12216 (1)
N(1)	6329 (5)	4425 (4)	8507 (2)
C(2)	5658 (6)	3462 (5)	8281 (3)
C(3)	5356 (6)	2772 (5)	8800 (3)
C(3A)	5870 (5)	3370 (5)	9413 (3)
N(4)	5800 (4)	3066 (4)	10046 (2)
C(4A)	6361 (6)	3804 (5)	10532 (3)
C(5)	6264 (6)	3522 (5)	11210 (3)
C(6)	6769 (6)	4213 (6)	11716 (3)
C(7)	7409 (6)	5235 (6)	11570 (3)
C(8)	7545 (5)	5557 (5)	10922 (3)
C(8A)	7004 (5)	4855 (5)	10362 (3)
C(9)	7114 (5)	5146 (5)	9675 (3)
C(9A)	6472 (5)	4413 (5)	9214 (3)
C(10)	6648 (6)	5411 (5)	8074 (3)
C(11)	7846 (6)	5211 (5)	7711 (3)
C(12)	7946 (6)	6185 (6)	7204 (3)
N(13)	9038 (6)	6121 (5)	6824 (3)
C(14)	8932 (8)	6880 (7)	6241 (4)
C(15)	10178 (8)	6434 (8)	7238 (4)
C(16)	4709 (6)	1666 (6)	8701 (3)
O(17)	4438 (5)	1184 (4)	9274 (2)
C(18)	3918 (9)	-43 (7)	9213 (3)
C(19)	2772 (12)	-121 (10)	9203 (8)
O(20)	4502 (5)	1137 (4)	8183 (2)
C(21)	5327 (6)	3307 (5)	7531 (3)
C(1P)	7856 (6)	6192 (5)	9510 (2)
C(2P)	7380 (6)	7299 (6)	9490 (3)
C(3P)	8122 (8)	8233 (6)	9306 (4)
C(4P)	9344 (8)	8042 (7)	9169 (4)
C(5P)	9862 (7)	6946 (8)	9198 (4)
C(6P)	9107 (6)	6018 (5)	9368 (3)
CL(')	1896 (2)	-977 (2)	6960 (1)
N(1')	3696 (5)	552 (4)	3408 (2)
C(2')	4377 (6)	1520 (5)	3235 (3)
C(3')	4677 (6)	2209 (5)	3787 (3)
C(3A')	4157 (5)	1650 (5)	4353 (3)
N(4')	4209 (4)	2007 (4)	5000 (2)
C(4A')	3631 (5)	1276 (5)	5413 (3)
C(5')	3705 (6)	1599 (5)	6119 (3)
C(6')	3187 (6)	919 (6)	6583 (3)
C(7')	2567 (6)	-106 (5)	6373 (3)
C(8')	2460 (6)	-471 (5)	5716 (3)
C(8A')	2991 (5)	222 (5)	5202 (3)
C(9')	2915 (5)	-126 (5)	4507 (3)
C(9A')	3544 (5)	610 (5)	4108 (3)
C(10')	3287 (7)	-384 (5)	2936 (3)
C(11')	2050 (9)	-128 (6)	2548 (4)
C(12')	1828 (9)	-1305 (8)	1961 (5)
N(13')	1103 (12)	-1104 (8)	1453 (5)
C(14')	869 (11)	-2120 (13)	1117 (7)
C(15')	269 (24)	-1075 (14)	1959 (11)
C(16')	5354 (6)	3332 (6)	3775 (3)
O(17')	5704 (4)	3768 (4)	4368 (2)
C(18')	6257 (8)	4974 (7)	4399 (4)
C(19')	7542 (9)	4926 (8)	4270 (4)
O(20')	5522 (5)	3840 (4)	3251 (2)
C(21')	4738 (7)	1623 (5)	2522 (3)
C(1P')	2181 (6)	-1196 (5)	4280 (2)
C(2P')	2728 (6)	-2291 (5)	4258 (3)
C(3P')	2016 (7)	-3259 (5)	4032 (3)
C(4P')	758 (8)	-3136 (7)	3867 (3)
C(5P')	201 (7)	-2075 (8)	3922 (4)
C(6P')	905 (7)	-1102 (6)	4126 (3)

Experimental Section

Melting points were taken in a capillary tube and are uncorrected. Uv spectra were determined in 95% EtOH using a Cary Model 14 spectrophotometer. Ir spectra were determined in Nujol using a Perkin-Elmer Model 421 recording spectrophotometer. NMR spectra were recorded on a Varian Model A-60A; chemical shifts were recorded in parts per million downfield from Me_4Si. Mass spectra were recorded using a CH-4 Atlas mass spectrometer. The silica gel used for chromatography was obtained from E. Merck A. G., Darmstadt, Germany.

Ethyl 7-Chloro-2-methyl-9-phenyl-1*H*-pyrrolo[3,2-*b*]quinoline-3-carboxylate (5). A mixture of 2-amino-7-chloro-5-phenyl-3*H*-[1,4]benzodiazepine (4,[13b] 30 g, 0.112 mol) and 300 ml of ethyl acetoacetate was heated at 145–160 °C (oil bath temperature) for 3 h. It was then evaporated in vacuo at 95 °C. The residue was triturated with ethyl acetate, and the resulting solid was filtered and washed with ethyl acetate followed by ether, 9.8 g of pale yellow needles, mp 300–302 °C. The analytical sample was prepared from ethyl acetate: mp 300 °C dec; uv sh 238 nm (ε 40 800), λ_{max} 249 (53 500), 334 (12 500), 354 (9500), sh 368 (8350); ir NH ~2900 (broad); C=O 1685 (s); C=N/C=C 1630, 1595, 1550, 1500; C–O/C–N 1265, 1170, 1155, 1140, 1085, 1040; aromatic 830, 780, 740, 700 cm^{-1}; NMR (Me_2SO-d_6) δ 10.71 (broad, 1, NH), 8.6 (d, 1, aromatic H, J = 9.5 Hz), 7.84–7.42 (m, 7, aromatic H), 4.4 (q, 2, OCH_2, J = 7 Hz), 2.8 (s, 3, NC–CH_3), 1.4 (t, 3, OC–CH_3, J = 7 Hz); mass spectrum m/e 364 (M^+).

Anal. Calcd for $C_{21}H_{17}ClN_2O_2$: C, 69.13; H, 4.70; Cl, 9.72; N, 7.68. Found: C, 68.79; H, 4.74; Cl, 9.79; N, 7.44.

***tert*-Butyl 7-Chloro-2-methyl-9-phenyl-1*H*-pyrrolo[3,2-*b*]quinoline-3-carboxylate (6).** A mixture of 4 (20 g, 0.0743 mol) and 200 ml of *tert*-butyl acetoacetate was heated for 2 h at 151 °C (oil bath temperature), and evaporated in vacuo (ca. 0.1 mm). The residue was triturated with ethyl acetate to give 3.35 g: mp 289 °C, raised to 292 °C dec on recrystallization from chloroform; uv λ_{max} 205 nm (ε 34 650), sh 238 (38 750), 252 (52 400), sh 320 (7400), 334 (12 400), 354 (9250), sh 367 (8150); ir NH ~2900 (broad); C=O 1685 (s); C–O/C=N 1635 (w), 1600 (w), 1550 (m), 1505, 1480; C–N/C–O 1270, 1150, 1140, 1090, 1020; aromatic 830, 795, 710, 700 cm^{-1}; NMR (pyridine-d_5) δ 2.83 (s, 3, NC–CH_3), 1.8 (s, 9, *tert*-butyl); mass spectrum m/e 392 (M^+).

Anal. Calcd for $C_{23}H_{21}ClN_2O_2$: Cl, 9.02; N, 7.13. Found: Cl, 8.90; N, 7.26.

The filtrate from the original trituration (from a run one-tenth the scale of the above) was evaporated and the residue chromatographed on 300 g of silica gel using 5% MeOH–$CHCl_3$. Fractions 1–4 (400 ml total) gave a trace (discarded). Fractions 5–7 (25 ml each) afforded 41 mg of **6** after crystallization from ether. Fractions 8–10 (25 ml each) were crystallized from CH_2Cl_2–ether to give 64 mg of **10**, mp 274–275 °C. It was identical with the authentic sample prepared below by condensation of 5-chloro-2-aminobenzophenone and ethyl (or *tert*-butyl) acetoacetate as shown by comparison of TLC, ir, uv, NMR, and mass spectrum.

7-Chloro-2-methyl-9-phenyl-1*H*-pyrrolo[3,2-*b*]quinol-3-yl Methyl Ketone (7) and 3-(7-Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)-4-hydroxy-3-penten-2-one (9). A mixture of **4** (2 g, 7.4 mmol) and 10 ml of acetylacetone was refluxed for 4 h and evaporated. The residue was chromatographed on 250 g of silica gel in 5% MeOH–$CHCl_3$. Fractions 1–2 (250 ml each) gave no material. Fractions 3–6 (25 ml each from now on) gave a trace (discarded). Fractions 7–8 gave 0.441 g of **9** which was crystallized twice from ether: 0.124 g, mp 175–176 °C; uv λ_{max} 218 nm (ε 28 200), sh 258 (14 100), sh 276 (10 200), 343 (25 500); ir C=O 1675, 1620, 1605, 1585, 1540, 1480; C–N/C–O 1355, 1325, 1320, 1220, 945; aromatic 835, 785, 740, 700 cm^{-1}; NMR ($CDCl_3$) δ 13.6 (broad, 1, OH), 7.62–7.06 (m, 8, aromatic H), 4.28 (broad, 2, CH_2), 2.62 (s, 3, $COCH_3$), 2.24 (s, 3, $=CCH_3$); mass spectrum m/e 352 (M^+).

Anal. Calcd for $C_{20}H_{17}ClN_2O_2$: C, 68.08; H, 4.86; Cl, 10.05; N, 7.94. Found: C, 67.82; H, 4.92; Cl, 10.06; N, 8.11.

Fractions 9–11 (ca. 0.8 g) were crystallized from ethyl acetate to give 0.278 g of **7**: mp 276–277 °C, raised on recrystallization to 278–279 °C dec; uv λ_{max} 209 nm (ε 27 500), 248 (63 000), 280 (22 500), sh 319 (7500), 333 (1210), 355 (10 000), 369 (8850); ir NH 3320; C=O/C=N 1640, 1630; C=N/C=C 1600, 1570, 1540, 1500; C–N 1300, 1160, 950; aromatic 820, 710 cm^{-1}; NMR (Me_2SO-d_6) δ 11.8 (broad, 1, NH), 8.07 (d, 1, aromatic H, J = 9.8 Hz), 7.8–7.43 (m, 7, aromatic H), 2.93 (s, 3, $COCH_3$), 2.74 (s, 3, NC–CH_3); mass spectrum m/e 334 (M^+).

Anal. Calcd for $C_{20}H_{15}ClN_2O$: C, 71.75; H, 4.52; Cl, 10.59; N, 8.37. Found: C, 71.74; H, 4.76; Cl, 10.48; N, 8.20.

Fraction 12 (0.398 g) was discarded. Fractions 13–14 (0.645 g) were crystallized from ether to give 0.179 g of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one, mp 213–214 °C. It was identical with an authentic sample[13c] as shown by mixture melting point and TLC.

7-Chloro-2-methyl-9-phenyl-1*H*-pyrrolo[3,2-*b*]quinoline-3-carboxylic Acid (8). The solid *tert*-butyl ester **6** (3.2 g, 8.17 mmol) was placed in a flask, cooled in ice, 62 ml of trifluoroacetic acid was added, and the mixture was allowed to stand at room temperature for 30 min. It was evaporated in vacuo (ca. 0.1 mm) at 30 °C and 100

ml of saturated aqueous sodium bicarbonate solution was added. The mixture was shaken; the resulting suspension filtered and the solid washed with water, then ether. Crystallization from CH_3OH–$CHCl_3$ gave 1.9 g of yellow needles, mp 296–297 °C dec. Second crop: 0.45 g; mp 295–296 °C; uv λ_{max} 204 nm (ϵ 31 500), sh 236 (39 550), 251 (56 800), 332 (12 850), 358 (9000), sh 372 (8100); ir NH/acid OH 3140 (broad), 3050, 2760, sh 2700; C=O 1700; C=C/C=N 1625, 1600, 1565; C–O/C–N 1290, 1175, 1165, 1135, 1075; aromatic 825, 775, 725, 700 cm^{-1}; NMR (Me_2SO-d_6) was poor owing to low solubility; mass spectrum *m/e* 336 (M^+).

Anal. Calcd for $C_{19}H_{13}ClN_2O_2$: C, 67.76; H, 3.89; Cl, 10.57; N, 8.32. Found: C, 67.48; H, 3.89; Cl, 10.78; N, 8.32.

Ethyl Ester of 7-Chloro-1-[3-(dimethylamino)propyl]-2-methyl-9-phenyl-1*H*-[3,2-*b*]quinoline-3-carboxylic Acid. Sodium hydride (0.421 g of 57% dispersion in mineral oil, 0.01 mol) was added to a solution of **5** (3.64 g, 0.01 mol) in 50 ml of DMF and the mixture was heated for 40 min at 95 °C. A solution of 3-dimethylaminopropyl chloride (1.21 g, 0.01 mol) in 1.21 g of xylene was added during 3 min, and heating continued overnight. The mixture was evaporated, H_2O and CH_2Cl_2 added, and the organic layer was shaken with aqueous 10% HCl. Since the resulting oily hydrochloride was not suitable for workup, the mixture was brought to pH 10 with 5% aqueous NaOH, the organic layer was separated, washed with saturated salt solution, dried ($MgSO_4$), and evaporated. The residue (3.3 g) was extracted with boiling ether (4 × 50 ml) and the extract concentrated to 25 ml to give 0.993 g of the product: mp 177–178 °C, raised to 179.5–180.5 °C on two recrystallizations from ether; uv sh 230 nm (ϵ 28 300), λ_{max} 256 (64 650), sh 322 (6500), 336 (11 950), 357 (9350), sh 370 (8200); ir *N*-alkyl 2810, 2780, 2760, 2720; C=O 1670; C=C/C=N 1610, 1590, 1545, 1485; C–O/C–N 1265, 1225, 1170, 1120, 1100; aromatic 830, 710 cm^{-1}; NMR ($CDCl_3$) δ 8.24 (d, 1, aromatic H, J = 8.5 Hz), 7.71–7.6 (m, 7, aromatic H), 4.54 (q, 2, OCH_2, J = 7 Hz), 3.85–3.5 (m, 2, *N*-pyrrole CH_2), 2.86 (s, 3, NC–CH_3), 2.06 [s, 6, $N(CH_3)_2$], 1.52 (t, 3, OC–CH_3), 1.76–1.25 (m, 4, CH_2CH_2N dialkyl); mass spectrum *m/e* 449 (M^+).

Anal. Calcd for $C_{26}H_{28}ClN_3O_2$: C, 69.40; H, 6.27; Cl, 7.88; N, 9.34. Found: C, 68.99; H, 6.34; Cl, 7.97; N, 9.19.

The residue from the original ether extraction and filtrates from the crystallization were combined and evaporated and the residue (2.5 g) chromatographed on 250 g of silica gel using 10% CH_3OH–$CHCl_3$. Fractions 1–3 (500 ml total) gave 0.5 g of starting material. Fraction 7 gave a mixture (discarded). Fractions 8–11 gave 1.4 g of the product. Crystallization from ether gave 0.943 g, mp 179–180 °C.

Synthesis of Compound 10.[14] A. Reaction of 2-Amino-5-chlorobenzophenone with Ethyl Acetoacetate. A mixture of 2-amino-5-chlorobenzophenone (23.2 g, 0.1 mol) and ethyl acetoacetate (52 g, 0.4 mol) was heated at 150–155 °C (oil bath temperature) for 3 h using a take-off condenser (15 ml was collected). The resulting suspension was cooled and the product filtered and washed with ether: 24 g (81% yield); mp 274–275 °C unchanged on crystallization from CH_2Cl_2; uv λ_{max} 207 nm (ϵ 35 450), 237 (39 400), 277 (6200), sh 330 (4400), 344 (5900), sh 356 (5250); ir =CH,NH,OH 3140, 2900 broad, 2730; C=O,C=N,C=C 1710 m, 1640 s, 1595, 1575, 1550; C–N/C–O 1405, 1350, 1085, 1080; aromatic 770, 710, 665 cm^{-1}; NMR (Me_2SO-d_6) δ 12.5 (broad, exchangeable with D_2O), 7.76–7.25 (m, 7, aromatic H), 7.0 (d, 1, aromatic H, J = 2.2 Hz), 2.25 (s, 3, CH_3); mass spectrum *m/e* 297 (M^+).

Anal. Calcd for $C_{17}H_{12}ClNO_2$: C, 68.56; H, 4.06; Cl, 11.91; N, 4.71. Found: C, 68.21; H, 4.10; Cl, 11.80; N, 4.80.

B. Reaction of 2-Amino-5-chlorobenzophenone with *tert*-butyl Acetoacetate. A mixture of 2-amino-5-chlorobenzophenone (4.61 g, 0.02 mol) and 46 ml of *tert*-butyl acetoacetate was refluxed for 2 h. The resulting suspension was filtered and the product washed with ether, 4.1 g (68% yield), mp 273.5–275 °C, raised to 274–275 °C on recrystallization from CH_2Cl_2. This compound was identical with the product obtained by condensation of 2-amino-5-chlorobenzophenone with ethyl acetoacetate as shown by comparison of TLC, uv, ir, NMR, and mass spectra.

Synthesis of 11. Sodium hydride (0.841 g of 57% dispersion in mineral oil, 0.02 mol) was added to a solution of **10** (5.94 g, 0.02 mol) in 100 ml of DMF and the mixture was heated at 95 °C for 30 min. A solution of 2-dimethylaminoethyl chloride (2.14 g, 0.02 mol) in 2.14 g of xylene was added, and heating continued for 18 h. The mixture was evaporated, H_2O and CH_2Cl_2 added, and the organic layer shaken with 10% aqueous HCl (ether added to break up emulsion). The resulting oily layer was separated by decantation, washed with CH_2Cl_2–ether (1:1), cooled, and basified. The product was extracted with CH_2Cl_2, and the solution washed with saturated salt solution, dried ($MgSO_4$), and evaporated. The residue was crystallized from ether to give 2.8 g: mp 155–156 °C, raised to 156–157 °C on recrystallization; uv λ_{max} 209 nm (ϵ 33 100), 239 (41 400), 282 (6200), sh 330 (4150), 345 (5750), sh 358 (4900); ir *N*-alkyl 2740; C=O 1705; C=O or C=N 1630; C=C 1600, 1585, 1555, 1485; C–N 1310, 1155, 1105; aromatic 810, 705 cm^{-1}; NMR ($CDCl_3$) δ 7.62–7.16 (m, 8, aromatic H), 4.48 (apparent t, 2, $CONCH_2$, apparent J = 7.5 Hz), 2.69 (apparent t, 2, CH_2N dialkyl, apparent J = 7.5 Hz), 2.4 (s, 3, $COCH_3$); mass spectrum *m/e* 368 (M^+).

Anal. Calcd for $C_{21}H_{21}ClN_2O_2$: C, 68.38; H, 5.74; Cl, 9.61; N, 7.60. Found: C, 68.30; H, 5.76; Cl, 9.83; N, 7.66.

***N*-Acetonyl-*N*-acetylacetamide** was prepared from glycine as described in the literature.[7] One distillation gave the product, bp 101–104 °C (0.08 mm). VPC indicated ca. 90% purity; NMR showed the presence of some *N*-acetonylacetamide.

***N*-Acetonylacetamide** was prepared by aqueous hydrolysis of *N*-acetonyl-*N*-acetylacetamide as described in the literature.[7] The product boiled at 103 °C (0.7 mm); VPC 98.98%; ir, mass spectrum were in accord; NMR ($CDCl_3$) δ 6.48 (broad, 1, NH), 4.18 (d, 2, CH_2, J = 5 Hz), 2.22 (s, 3, $NCOCH_3$), 2.05 (s, 3, C–$COCH_3$).

Reaction of 2-Amino-5-chlorobenzophenone with *N*-Acetonylacetamide. A mixture of 2-amino-5-chlorobenzophenone (11.9 g, 0.0515 mol) and *N*-acetonylacetamide (23.8 g, 0.206 mol) was heated at 170 °C (oil bath temperature) for 4 h using a take-off condenser (1.1 ml was collected). The residue was chromatographed on 2 kg of silica gel using 5% MeOH–$CHCl_3$. Fractions 1–9 (3.85 l. total) gave no material. Fractions 10–14 (250 ml each from now on) gave a trace of oil. Fractions 15–17 gave 2.8 g of *N*-[(6-chloro-4-phenyl-2-quinolyl)methyl]acetamide (**16**), which was crystallized from CH_3OH: 2.3 g, mp 167.5–168.5 °C; uv λ_{max} 234 nm (ϵ 50 500), 290 (8000), sh 310 (5420), 325 (4460); ir NH=CH 3320, 3060; C=O 1645; C=C/C=N 1590, 1570, 1540, 1485; C–N 1355, 1345, 1290, 1030; aromatic 835, 765, 715, 710 cm^{-1}; NMR ($CDCl_3$) δ 8.13–7.39 (m, 8, aromatic H), 7.24 (s, 1, C_3H), ~7.24 (broad, 1, NH), 4.71 (d, 2, CH_2, J = 5 Hz), 2.12 (s, 3, CH_3); mass spectrum *m/e* 310 (M^+).

Anal. Calcd for $C_{18}H_{15}ClN_2O$: C, 69.56; H, 4.87; Cl, 11.41; N, 9.02. Found: C, 69.63; H, 4.97; Cl, 11.48; N, 9.13.

Fractions 18–21 gave 1.9 g of a mixture. Fractions 22–72 gave 8.6 g of *N*-(6-chloro-2-methyl-4-phenyl-3-quinolyl)acetamide (**15a**), which was crystallized from MeOH, 6.7 g, mp 181–182 °C. Second crop: 1.3 g, mp 178–180 °C; uv sh 210 nm (ϵ 31 750), λ_{max} 233 (45 950), 282 (5850), sh 296 (5000), 311 (4100), 326 (4300); ir NH 3250; C=O/amide II 1655, 1605, 1585, 1570, 1560, 1505, 1480; C–N 1275, 1270, 1040; aromatic 840, 710 cm^{-1}; NMR ($CDCl_3$) δ 8.05–7.08 (m, 9, aromatic H and NH), 2.64 (s, 3, N=CCH_3), 1.88 (s, 3, $COCH_3$); mass spectrum *m/e* 310 (M^+).

Anal. Calcd for $C_{18}H_{15}ClN_2O$: C, 69.56; H, 4.87; Cl, 11.41; N, 9.02. Found: C, 69.70; H, 5.05; Cl, 11.51; N, 9.23.

3-Amino-6-chloro-2-methyl-4-phenylquinoline (15b). A mixture of **15a** (1.02 g, 3 mmol), sodamide (0.82 g, 21 mmol), and 10 ml of freshly distilled *N,N*-diethylaniline was refluxed for 1.75 h. A lightly colored suspension resulted. It was cooled in ice, 10 ml of H_2O was added, and after stirring for 15 min, the mixture was extracted with ether (4 × 25 ml). The organic solution was washed with saturated salt solution, dried ($MgSO_4$), and evaporated, toward the end at 0.1 mm and 95 °C, to give 0.9 g. Crystallization from ether gave 0.298 g of recovered starting material. The filtrate was evaporated and the residue chromatographed on 60 g of silica gel using 5% MeOH–$CHCl_3$. Fractions 1–4 (200 ml total) gave no material. Fractions 5–6 (10 ml from now on) gave 0.205 g of diethylaniline. Fractions 7–8 gave 0.23 g of **15b**. Crystallization from ether gave 90 mg, mp 141–142 °C. Second crop: 130 mg, mp 140–141 °C; uv λ_{max} 206 nm (ϵ 24 900), 219 (26 800), 249 (42 800), sh 279 (5350), sh 290 (4300), sh 302 (2870), 349 (6860); ir NH 3460, 3360; NH def, C=C,C=N 1625, 1605, 1585, 1505, 1490; aromatic 875, 820, 715 cm^{-1}; NMR ($CDCl_3$) δ 8.0–7.17 (m, 8, aromatic H), 3.78 (broad s, 2, NH_2, exchanges with D_2O), 2.65 (s, 3, CH_3); mass spectrum *m/e* 268 (M^+).

Anal. Calcd for $C_{16}H_{13}ClN_2$: C, 71.51; H, 4.87; Cl, 13.19; N, 10.43. Found: C, 71.44; H, 4.90; Cl, 13.29; N, 10.34.

***N*-(6-Chloro-2-methyl-4-phenyl-3-quinolyl)diacetamide (15c).** A mixture of **15a** (2 g, 6.45 mmol) and 5 ml of acetic anhydride was refluxed for 19 h. The resulting solution was allowed to crystallize. The product was recrystallized from ether to give 1.68 g of **15c**: mp 160–161 °C; uv sh 216 nm (ϵ 40 250), λ_{max} 235 (54 450), 281 (5850), sh 300 (4300), 314 (3850), 328 (4500); ir C=O 1725, 1695; C=C/C=N 1610, 1580, 1560, 1480; C–N 1280, 1265, 1230, 1020; aromatic 835, 715 cm^{-1}; NMR ($CDCl_3$) δ 8.18–7.0 (m, 8, aromatic H), 2.6 (s, 3, N=CCH_3), 2.15 (s, 6, 2 $COCH_3$); mass spectrum *m/e* 352 (M^+).

Anal. Calcd for $C_{20}H_{17}ClN_2O_2$: C, 68.08; H, 4.86; Cl, 10.05; N, 7.94. Found: C, 68.43; H, 4.93; Cl, 10.05; N, 7.94.

***N*-(6-Chloro-2-methyl-4-phenyl-3-quinolyl)acetamide 1-Oxide.** A solution of **15a** 5.25 g, 0.017 mol) and *m*-chloroperbenzoic

acid (85%, 3.45 g, 0.017 mol) in 75 ml of CH_2Cl_2 was stirred at room temperature for 6 h. The resulting suspension was filtered and the solid washed with saturated $NaHCO_3$ solution. The filtrate was separated, and the organic layer was washed with $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated. The residue was combined with the above solid and crystallized from MeOH: 4.63 g, mp 257–258 °C, raised to 259–260 °C on recrystallization; uv sh 224 nm (ϵ 26 300), λ_{max} 236 (32 100), 252 (35 250), 331 (10 900); ir NH=CH 3150, 3080, 2770; C=O 1685; C=C/C=N amide II 1600, 1585, 1560, 1515, 1500, 1480; C–N/N–O 1330, 1265, 1205, 1175, 1105; aromatic 830, 710 cm^{-1}; NMR (Me_2SO-d_6) δ 7.94–7.22 (m, 8, aromatic H), ~3.24 (broad, 1, NH), 2.49 (s, 3, N=CCH_3), 1.85 (s, 3, $COCH_3$); mass spectrum *m/e* 326 (M^+).

Anal. Calcd for $C_{18}H_{15}ClN_2O_2$: C, 66.16; H, 4.63; Cl, 10.85; N, 8.57. Found: C, 65.91; H, 4.71; Cl, 10.85; N, 8.57.

X-Ray Structure Determination of the 1-[3-(Dimethylamino)propyl] Derivative of 5. A. Crystal Data. The crystals are triclinic, clear prisms; space group $P\bar{1}$; a = 10.597 (2) Å; b = 11.402 (1) Å; c = 19.810 (1) Å; α = 91.08 (1)°; β = 93.99 (1)°; γ = 90.11 (2)°; V = 2387.6 (4) Å^3; Z = 4; ρ_{calcd} = 1.25 g/cm^3. Cell parameters were calculated by least squares from accurately determined Kα_1 2θ values for 19 selected high angle reflections.

Intensity data were collected on a Syntex $P\bar{1}$ diffractometer controlled by an IBM 1800 computer. The θ–2θ scan technique was used with graphite-monochromatized Cu Kα radiation. A 2θ range of 3° was scanned at a variable rate (4–10° per minute) depending on the intensity of the reflection being measured. The total time spent counting background—half at each end of the scan—was equal to the time spent scanning. The crystal orientation was determined by the computer before data collection using seven orienting reflections. Data were limited to 2θ less than 100° because crystal quality was not very good (in the range 2θ = 90–100°, the mean $I/\sigma(I)$ was only 1.7). Ten reflections were monitored periodically during the data collection; a slight loss in intensity (4%) was noted. Standard deviations in observed intensities were approximated by the function $\sigma(I) = [\sigma^2(I)\ counting\ statistics + (0.019\ I)^2]^{1/2}$ where the coefficient of I in the last term was calculated from those deviations in the check reflection observations (after deterioration correction) which were not explained by counting statistics. The usual Lorentz correction was applied[15] along with a polarization correction appropriate for a monochromator with 50% perfect character.[16] The final reduced set (4914 reflections) contained a large number of very weak reflections, including 655 which are negative intensity observations (scaled background counts exceeded scan counts).

B. Trial Solution. A trial solution was obtained by direct methods,[17] with some effort, using the DIREC program written by one of the authors (D.J.D.). The 19th E map phased by this automatic program clearly showed 41 of the 64 nonhydrogen atoms; the rest were easily found by tangent formula extension of phases of structure factors calculated from these trial atoms. The successful E map was calculated with phases from an extension of the seventh highest ranking set of phases from the third symbolic addition (reflections $\bar{3}$,2,0; 3,3,$\bar{6}$; and $\bar{2}$,1,1 were used to define the origin, and reflections $\bar{2}$,2,0; $\bar{3}$,1,$\bar{2}$; $\bar{2}$,1,$\bar{1}$; 4,1,$\bar{1}\bar{0}$; and $\bar{5}$,1,16 were assigned symbolic phases).

C. Refinement. Coordinates, thermal parameters, and the scale factor were refined by multiple-matrix least squares. The function minimized was $\Sigma w(F_o^2 - F_c^2)^2$.

Weights w were taken equal to the reciprocals of the variances $\sigma^2(F_o^2)$ determined at data reduction time and scaled by propagation of error through subsequent corrections. All reflections were used in the refinement regardless of size. Reflections with negative observed intensity were used in the refinement as negative $|F_o|^2$. Atomic form factors are from International Tables for X-Ray Crystallography,[18] except for hydrogen, which was taken from Stewart, Davidson, and Simpson.[19]

The symmetry-independent molecules have a pseudosymmetric relationship (which holds to within 0.8 Å), of $1 - x$, $\frac{1}{2} - y$, $-\frac{1}{2} + z$. If this relationship were exact, the space group would be $P2_1/b$. In the matrix scheme for the final refinement, coordinates were in two matrices, with like parts of each molecule in the same matrix (because of pseudosymmetric correlations). The scale factor and the anisotropic thermal parameters of the chlorines were in another matrix, and the remainder of the anisotropic thermal parameters were in individual (6 × 6) block matrices. Hydrogen parameters were not refined, but were added to structure factor calculations. Positions for the C(21) methyl hydrogens were found in a difference Fourier map. Coordinates for the other hydrogen atoms were calculated assuming standard (tetrahedral or planar) orientations. Hydrogen isotropic temperature factors were fixed about ½ unit higher than attached carbons. The dimethylamino group in the primed molecule appears to be disordered, since atoms in this region refined to coordinates with unreasonable distances and angles and thermal parameters with largest principal axes from 0.6 to 0.9 Å. An effort was made to find a model for the disorder. A difference Fourier map, with C12′–C15′ out of the calculations, showed large peaks at chemically reasonable positions, but no reasonable alternate model using the smaller peaks. Upon refinement, the dimethylamino atoms moved back to their original locations. A difference Fourier map with all atoms in the structure factor calculations showed no extraneous peaks of larger size than hydrogens. Refinement was considered converged when all shifts were less than ¼ standard deviations, except for parameters of the dimethylamino group in the primed molecule where some shifts were as large as standard deviations.

The final agreement indices for all 4914 reflections are R = 0.123 ($R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$); weighted $R = [\Sigma w(|F_o|^2 - |F_c|^2)^2/\Sigma w|F_o|^4]^{1/2}$ = 0.128; and standard deviation of fit = $[\Sigma w(|F_o|^2 - |F_c|^2)^2/m - s]^{1/2}$ = 1.66. For the 1471 reflections with F_o^2 greater than 3 standard deviations, R is 0.048 and weighted R is 0.097.

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Registry No.—**4,** 7564-07-0; **5,** 58375-02-3; **5** 1-(3-dimethylaminopropyl) derivative, 58375-03-4; **6,** 58375-04-5; **7,** 58375-05-6; **8,** 58375-06-7; **9,** 58375-07-8; **10,** 58375-08-9; **11a,** 58375-09-0; **11b,** 58375-15-8; **15a,** 58375-10-3; **15b,** 58375-11-4; **15c,** 58375-12-5; **16,** 58375-13-6; ethyl acetoacetate, 141-97-9; *tert*-butyl acetoacetate, 1694-31-1; acetylacetone, 123-54-6; 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one, 1694-78-6; 3-dimethylaminopropyl chloride, 109-54-6; 2-amino-5-chlorobenzophenone, 719-59-5; *N*-acetonyl-*N*-acetylacetamide, 51862-97-6; *N*-acetonylacetamide, 7737-16-8; *N*-(6-chloro-2-methyl-4-phenyl-3-quinolyl)acetamide 1-oxide, 58375-14-7.

Supplementary Material Available. Tables of H atom coordinates and anisotropic temperature factors (2 pages). Ordering information is given on any current masthead page.

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Barriers to Nitrogen Inversion in Cyclic and Acyclic Substituted Hydroxylamines. A Theoretical Study[1]

Daniel Kost*

Department of Chemistry, Ben Gurion University of the Negev, Beersheva, Israel

Morton Raban[2]

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

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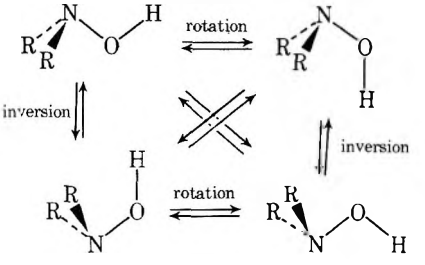
Approximate SCF-MO calculations (CNDO/2) have been used to study nitrogen inversion in *N,N*-dimethylhydroxylamine. The difference between the barriers in cyclic and acyclic substituted hydroxylamines was simulated by calculating the inversion barrier as a function of dihedral angle. Excellent agreement between calculated and experimental barriers was found. The results obtained have provided evidence for an inversion-dominated topomerization in dialkyl- and trialkylhydroxylamines and for rate retardation due to lone pair–lone pair interactions as well as the electronegativity of oxygen.

Numerous experimental investigations of barriers to conformational interchange in cyclic and acyclic hydroxylamines have been carried out[3-5] and have also been the subject of theoretical interest.[6] Chemical shift nonequivalence of diastereotopic groups in these systems can arise from slow inversion of the nitrogen pyramid or slow torsion about the nitrogen–oxygen single bond since both processes are required for topomerization (Scheme I). In cyclic hydroxylamines

Scheme I.



R = CH_3

where the nitrogen and oxygen atoms form part of three-,[4,7] four-,[8] or five[9]-membered rings the rate-determining step must be inversion of the nitrogen pyramid, since the ring system constrains the N–O bond to a planar or nearly planar geometry, which is very close to the transition state for torsion. Very substantial barriers to nitrogen inversion are observed in these systems. The presence of the oxygen atom greatly increases the barriers, and oxaziridines exhibit the highest nitrogen inversion barriers which have been measured.

The acyclic hydroxylamine derivatives represent a more ambiguous case. Here, either torsion or inversion could be the rate-determining step. It has been argued that slow nitrogen inversion is the rate-determining step in the topomerization of trialkylhydroxylamines,[10] while in other hydroxylamine systems, evidence for substantial torsional barriers has been obtained.[5,11] A third possibility which may be considered is that torsion and inversion occur synchronously rather than sequentially and that the transition state for the topomerization involves both flattening of the nitrogen pyramid and torsion about the N–O bond.

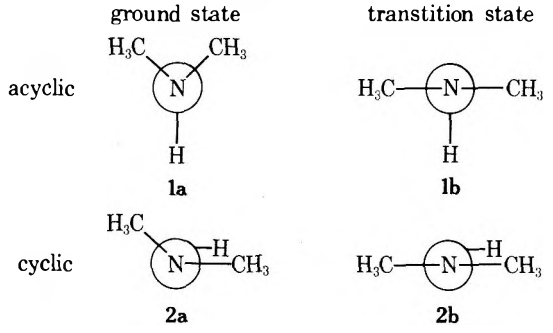
It is clear that the presence of an oxygen atom bonded to nitrogen has an important effect in raising the barrier to nitrogen inversion. However, the precise reasons for this effect are not entirely clear. The electronegativity of the oxygen atom and the presence of nonbonding valence electrons are two features of the oxygen atom which have been implicated. Both theoretical[12] and experimental[13] evidence have been obtained for increased barriers to nitrogen inversion as a function of the increased electronegativity of the atom bonded to nitrogen. Interactions between lone pairs of valence electrons on adjacent atoms might also lead to increased nitrogen inversion barriers. Overlap between filled valence level orbitals should lead to destabilization and this destabilization should be greatest in the transition state for nitrogen inversion since the increased p character of the nitrogen lone pair orbital should facilitate π overlap.

Comparison between cyclic and acyclic analogues can provide one means of distinguishing between these two possibilities. If electronegativity alone were important we would expect to find the nitrogen inversion barrier to be independent of the N–O dihedral angle since the inductive potency of the oxygen atom should not be affected by the torsion angle. If, on the other hand, π overlap between vicinal pairs of nonbonded valence electrons is most important we would expect to find that the nitrogen inversion barrier is a strong function of dihedral angle. Since the interaction is repulsive, the adoption of a geometry of minimum interaction, which is possible only for the acyclic examples, should lead to lowered nitrogen inversion barriers. Indeed, comparisons of this sort between experimentally obtained barriers for cyclic and acyclic trialkylhydroxylamines indicated that the barriers in the acyclic compounds are ca. 3 kcal/mol lower than in their cyclic analogues.[5] Barriers to nitrogen inversion in acyclic hydrazines also appear to be substantially lower than in cyclic hydrazines.[14]

These comparisons suffer from the drawback that not all parameters can be effectively controlled. Thus, steric interactions and ring strain are known to have large effects on nitrogen inversion barriers, and it is not possible to devise model cyclic and acyclic compounds in which differences in steric interactions are removed and in which ring strain effects are avoided. For this reason the conclusions based upon experimental comparisons are not completely definitive. A more conclusive comparison would have to involve cyclic and acyclic models in which all molecular parameters would be identical except for the dihedral angle associated with the nitrogen–oxygen bond. While such models are not accessible experimentally, such a comparison between calculated inversion barriers can be realized using molecular orbital calculations. This paper reports the results of such a study of barriers to nitrogen inversion in *N,N*-dimethylhydroxylamine using CNDO/2 SCF-MO calculations. The geometries used for the acyclic ground state (**1a**) and transition state (**1b**) and the cyclic ground state (**2a**) and transition state (**2b**) were those in Scheme II.

Method of Calculation. CNDO/2 calculations were carried out using the CNINDO program.[15] Geometry optimization was

Scheme II



performed for the N–O, O–H and C–N bond lengths and for the C–N–C and N–O–H bond angles in the ground state and in the transition state. The angle between the O–N bond and the C–N–C plane (nitrogen out of plane angle) was also optimized for the ground state. The geometry of the methyl hydrogens was not optimized but held fixed throughout the calculations. The methyl H–C–H and H–C–N bond angles were precisely tetrahedral, and the C–N torsion angles were such that two of the hydrogen atoms lay in the CNC plane and these atoms H–C–N–C–H traced out a W shape. The bond lengths and angles are given in Table I. The same bond lengths and angles were used for the cyclic model except for the C–N–O–H dihedral angle, which was set equal to 0° (eclipsed methyl group and hydrogen). The original parameters of the CNINDO program were used throughout the calculations.

Results and Discussion

The energies of both the pyramidal ground state and the planar transition state were calculated as a function of the torsion angle. These data are given in Table II and are plotted in Figure 1.[17] Two different representations for the torsion angle can be used: ϕ, the dihedral angle between the O–H bond and one of the N–C bonds, and θ, the dihedral angle between the O–H bond and the bisector plane of the C–N–C angle, which also corresponds to the dihedral angle between the O–H bond and the nitrogen lone pair orbital. Since the latter is of greater significance in terms of lone pair interactions, the data in Figure 1 are plotted in terms of θ.

The lone pair interactions between oxygen and nitrogen are best considered by dividing the lone pair density on oxygen into two nonequivalent lone pair orbitals. One of these orbitals is the pure p orbital which has its axis at right angles to the N–O–H plane; the other is a hybrid orbital in the N–O–H plane which has approximately sp hybridization ($sp^{0.8}$ for an N–O–H angle of 107°).[18] If we consider π overlap between the lone pair orbital on nitrogen and the lone pair orbitals on oxygen, it is clear that π overlap with the pure p orbital must be much more important than that with the hybrid orbital. Minimum overlap will then occur when the nitrogen lone pair lies within the N–O–H plane, i.e., when $\theta = 90°$.

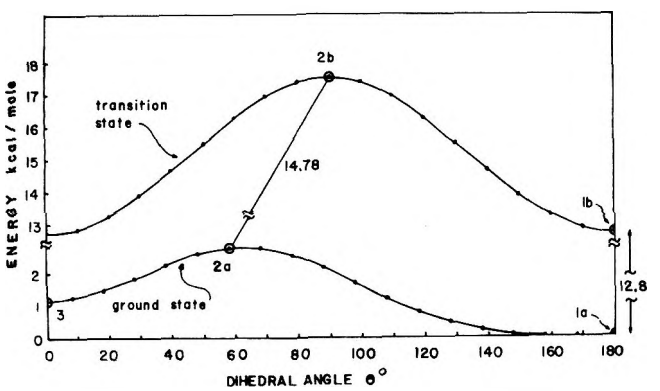


Figure 1. CNDO/2 calculated energy profiles for N–O torsion for the pyramidal (ground) and planar (transition) states of dimethylhydroxylamine.

Table I.[a] Geometry of *N,N*-Dimethylhydroxylamine, Optimized with Respect to Minimum Energy

	Ground state	Transition state
Bond lengths, Å		
O–H	1.04	1.04
N–O	1.30	1.29
C–N	1.42	1.41
C–H	(1.093)	(1.093)
Bond angles, deg		
N–O–H	107	108
C–N–C	107	122
Dihedral angle between N–O and C–N–C plane, deg	123	(180)

[a] Bond lengths and angles in parentheses were not adjusted to provide minimum energy.

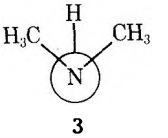
Table II. Change of Calculated Total Energy as a Function of Dihedral Angle

Ground state			Transition state		
ϕ^a	θ^b	E^c	E^c	θ^b	ϕ^a
−58.2	0	1.16	12.74	0	90
−50	8.2	1.23	12.87	10	80
−40	18.2	1.47	13.26	20	70
−30	28.2	1.84	13.88	30	60
−20	38.2	2.24	14.64	40	50
−10	48.2	2.59	15.48	50	40
0	58.2	2.78	16.28	60	30
10	68.2	2.77	16.95	70	20
20	78.2	2.54	17.40	80	10
30	88.2	2.16	17.56	90	0
40	98.2	1.68	17.40	100	−10
50	108.2	1.21	16.95	110	−20
60	118.2	0.78	16.28	120	−30
70	128.2	0.46	15.48	130	−40
80	138.2	0.23	14.64	140	−50
90	148.2	0.1	13.88	150	−60
100	158.2	0.03	13.26	160	−70
110	168.2	0.01	12.87	170	−80
121.8	180.	0	12.74	180	−90

[a] HONC dihedral angle. [b] Dihedral angle between OH and CNC bisector. [c] Total energy (kcal/mol) relative to the energy of the minimum energy ground state conformation.

As the data indicate, both geometries exhibit torsional barriers, although these barriers are considerably smaller than those expected on the basis of the barriers measured experimentally for *N*-phenyl and *N*-acylhydroxylamines,[5,9] or obtained using ab initio calculations.[6]

In both cases energy minima are found which correspond to eclipsing of the O–H bond with the nitrogen lone pair orbital (i.e., corresponding to $\theta = 0$ and 180°), geometries of minimum π overlap between lone pair orbitals on oxygen and nitrogen. This is in accord with suggestions based upon variable temperature NMR spectra of *N*-alkoxy-2-piperidones.[5] While the curve for the planar transition state is symmetrical, that for the ground state is unsymmetrical since two geometries are possible, **1a** and **3**, in which the O–H bond eclipses the nitrogen lone pair. While both represent local minima, the



3

Table III. Calculated and Experimental Nitrogen Inversion Barriers in Substituted Hydroxylamines

State	CNDO/2 barrier[a]	Exptl barriers
Acyclic	12.7	12.8[c]
Cyclic[b]	14.8	15.6[d]

[a] Difference between calculated total energies for the ground and transition states (kcal/mol). [b] The cyclic state means full eclipsing of CH_3 and H. Variation of the dihedral angle by 10° in either direction caused changes in total energy of ca. 0.2 kcal/mol. [c] Barrier for *N,N*-dibenzylhydroxylamine in $CDCl_3$ from ref 10c. [d] Barrier for *N*-methylisoxazolidine in $CDCl_3$ from ref 9a.

conformer **1a**, whose Newman projection resembles a Y, is of lower energy than conformer **3** (which has been referred to as the W conformer[6c]). It is noteworthy that ab initio calculations[6] on hydroxylamine itself and on the related isoelectronic anion $^-CH_2OH$ have also indicated that the Y conformer is more stable than the W conformer. An x-ray crystallographic structure determination of a related compound, a sulfenamide, similarly featured a Y conformation along the N–S bond in the Newman projection.[20]

The ground state conformation **2a** serves as a cyclic model and has dihedral angles of $\phi = 0°$ and $\theta = 58.2°$. This point lies very close to the torsional energy maximum which occurs at $\phi = 5°$, $\theta = 63°$. Thus, the judgment[5] that the geometry in cyclic compounds corresponds to a point near the torsional maximum and to a geometry of maximum repulsive interaction seems to be supported. We may note also that the calculated torsional barrier is higher for the transition state than for the ground state as predicted by the model discussed above, since increased p character in the nitrogen lone pair orbital should result in greater overlap with the oxygen lone pair p orbital in the torsional transition state.

The nitrogen inversion barriers are obtained by taking differences between points on the two curves in Table II or Figure 1. Vertical lines in Figure 1 represent inversion barriers under the constraint that θ remain a constant. This is satisfactory for **1** since both the ground state and transition state have values of $\theta = 180°$; the value of ϕ, however, changes from 121.8° in **1a** to 90° in **1b**. By contrast, the inversion of the cyclic model is characterized by a change in θ from 58.2° in **2a** to 90°, while ϕ remains unchanged at 0° for both ground and transition states. For this reason the inversion of **2** is not represented by a veritcal line in Figure 1 but by an oblique line.

The values for the inversion barriers as calculated by CNDO/2 are given in Table III. The agreement of the CNDO/2 values with experimental values is surprisingly good. The experimental barriers obtained by variable temperature NMR spectroscopy for the similar compounds *N,N*-dibenzylhydroxylamine[10c] and *N*-methylisoxazolidine[9a] are given in Table III for comparison purposes. We have also calculated the inversion barriers using two other semiempirical methods, INDO and the modification of CNDO developed by Mislow and co-workers for the calculation of pyramidal inversion barriers.[13b] However, the CNDO/2 optimized geometry was used with these methods, resulting in barriers which are much too low (INDO cyclic model barrier 5.2 kcal/mol; acyclic 1.6 kcal/mol. Modified CNDO cyclic model barrier 3.8 kcal/mol; acyclic 2.4 kcal/mol). Apparently this procedure is inadequate, and individual geometry optimization with each method is essential in order to obtain acceptable results. In spite of this fact, the same general trend to higher barriers for the cyclic models is evident by both of these methods, lending further support to the conclusion derived from this trend as calculated using the CNDO/2 method.

The mechanism for stereomutation or topomerization of substituted hydroxylamines has been a matter of some controversy. Both inversion of the nitrogen pyramid and torsion about the N–O bond are required for interconversion of a chiral hydroxylamine and its mirror image (degenerate racemization). Since either step could conceivably be the rate-determining step the topomerization can be described as rotation dominated[6e] if the reaction coordinate in the neighborhood of the transition state primarily describes torsion about the N–O bond or inversion dominated if the reaction coordinate involves predominantly changes in pyramidality at nitrogen. A number of experimental probes have been used to distinguish between rotation-dominated and inversion-dominated topomerization in the sulfur analogues of hydroxylamines, the sulfenamides.[20,21] In the sulfenamide series the experimental results have demonstrated conclusively that the topomerization is rotation dominated, except in the sulfenylaziridines where inversion-dominated topomerization is found.[22] The experimental data in the hydroxylamine system have been far more ambiguous. Initial results on substituent effects on inversion barriers in trialkylhydroxylamines seemed to favor a rotation-dominated mechanism.[23] Subsequent studies have indicated that other substituent effects favor inversion-dominated topomerization.[10c] In our view, the present close agreement between calculated and observed barriers provides further support for the assignment of an inversion-dominated mechanism for topomerization of dialkyl- and trialkylhydroxylamines.

Table IV. Eigenvectors for the HOMO of 2b

Atom	Atomic orbital[a]	Eigenvector
O	p_z	0.4298
N	p_z	−0.7721
C_1	p_z	0.1142
C_2	p_z	0.1158
H-(O)	s	0
H_1	s	0
H_2	s	−0.2190
H_3	s	0.2190
H_4	s	0
H_5	s	0.2200
H_6	s	−0.2200

[a] The AO's which are not listed had zero Eigenvectors.

The results rule out the possibility that inversion and rotation take place simultaneously in acyclic hydroxylamines with a common planar transition state (the diagonal path in Scheme I). Such a transition state would correspond to the cyclic conformation **2b**. The data in Table II and Figure 1 indicate that the energy of **2b** is substantially higher than that of either **1b** or **2a**, which are the transition state conformations for nitrogen inversion and N–O torsion in the acyclic molecule.

Examination of the molecular orbitals calculated for the cyclic transition state **2b** further indicates the importance of π overlap of the lone-pair p orbitals on nitrogen and oxygen. In this conformation all of the atoms except the methyl hydrogen atoms lie in the XY plane, and hence an analysis of the contribution of each of the isoalted atomic orbitals to the moelcular orbitals can be made. The highest occupied molecular orbital (HOMO) of **2b** clearly corresponds to antibonding π interaction of the p_z orbitals of the nitrogen and oxygen atoms (Table IV). This destabilizing interaction obviously becomes smaller as the dihedral angle between the p_z orbitals is changed, and the overlap reduced.

Our results also provide more convincing evidence that repulsive interactions between nonbonded valence electrons play a role in raising barriers to nitrogen inversion in cyclic hydroxylamines and, by extension, in related systems including substituted hydrazines. This is clearly not the only

source of the rate retardation: the high barriers calculated and measured for acyclic hydroxylamines indicate that the electronegativity of the oxygen atom also plays a very important role.

Registry No.—*N,N*-Dimethylhydroxylamine, 5725-96-2; *N,N*-dibenzylhydroxylamine, 621-07-8; *N*-methylisoxazolidine, 2244-44-9.

References and Notes

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Regiospecific Synthesis of Unsymmetrical Azoxy Compounds (Diazene *N*-Oxides)[1a]

Victor Nelson,[1b] Arthur Serianz,[1b] and Peter Kovacic*

Department of Chemistry, University of Wisconsin—Milwaukee, Milwaukee, Wisconsin 53201

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A directed synthesis is described of unsymmetrical azoxy compounds by condensation of nitroso substrates with *N,N*-dihaloamino derivatives in the presence of different types of promoters. Products bearing a variety of substituents, including aryl, alkyl, carboxylate, carbonamide, and halogen groups, are produced in fair to high yield. Evidence is presented that the reaction can proceed by several mechanistic pathways, depending upon the promoter.

Until 1974 there were only two useful methods for the regiospecific synthesis of azoxyalkanes and alkylazoxyarenes.[2,3] Other methods are not regiospecific[4a,b] or are impractical when electron-withdrawing groups are present.[4c] Recently,[5] we described the regiospecific synthesis of azoxyalkanes and alkylazoxyarenes by condensation of an *N,N*-dichloro amine with a nitroso compound in the presence of caustic (eq 1)

$$RNCl_2 + R'NO \longrightarrow RN{=}N(O)R' \qquad (1)$$

but the method is not useful if product or starting material is sensitive to basic conditions.

We herein report that the condensation of *N,N*-dihalo amine derivatives and tertiary alkyl or aryl nitroso compounds can be effected by a wide variety of promoters, generally in fair to excellent yields. It is probable that several mechanistic pathways pertain, depending upon the promoter.

Results and Discussion

By the condensation of a tertiary alkyl or aryl nitroso substrate with an *N,N*-dihalo amine derivative, various types of azoxy compounds (Table I) have been prepared. In addition to the base-sensitive ester (**3**), amide (**5**), and acyl derivative (**4**), we have synthesized members containing two azoxy moieties (**10** and **11**) (Table II), and the interesting compound "chloroazoxobenzene" (**8**) in a yield superior to that reported in the only other published procedure.[6]

The method also works with *N,N*-dibromo compounds as shown in Table III. Only two dibromoamino derivatives, a dibromo amide and dibromo amine, were investigated. In general *N,N*-dibromo substrates provide considerably higher yields than the corresponding *N,N*-dichloro counterparts. The *N,N*-dibromo amide, however, gave poorer results, presumably owing to its instability (decomposition even below 0 °C). This method for the synthesis of azoxy compounds is limited mainly by the availability of the nitroso precursor and the lack of success with aromatic *N*-halo amines. An attempt by us to N,N-dichlorinate *m*-nitroaniline was not fruitful, and exposure of sulfanilic acid to hypochlorite yielded the corresponding azo compound.[7]

Since primary and secondary nitrosoalkanes preferentially exist as the oxime tautomers, we were able to use only tertiary alkyl or aryl nitroso compounds. With the intent of circumventing this deficiency, we prepared the haloazoxy compounds **6** and **12** in order to replace subsequently the halogen with hydrogen. Attempted reductions with Zn, $CrCl_2$, Bu_3SnH, $NaBH_4$, and HI yielded intractable material in all cases. Sodium cyanoborohydride proved to be unreactive, even toward the azoxy moiety.

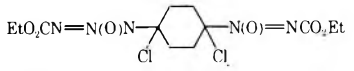
A convenient synthesis of azoxyalkenes is desirable, since several natural products[8] such as **13** contain α,β unsaturation, for which type there are only a few published syntheses.[9] Experiments aimed at producing such compounds from pre-

Table I. Diazene *N*-Oxide Syntheses

Product	Promoter	R′N(O) = NR: R	R′	Yield, %
1[a]	CuCl	*n*-Bu	Ph	83
2[a]	CuCl	C_6H_{11}	Ph	58
3	CuCl	CO_2Et	Ph	65
3	CuCN	CO_2Et	Ph	90
3	KI	CO_2Et	Ph	71
4	CuCl	PhCO	Ph	75
5	CuCl	Me_2NCO	Ph	51
6	CuCl	*t*-Bu		38
7[a]	CuCl	*t*-Bu	Ph	44
7	KI	*t*-Bu	Ph	79
8	CuCN	Cl	Ph	25
8	KI	Cl	Ph	60
9	CuCN	PhCO	*t*-Bu	25

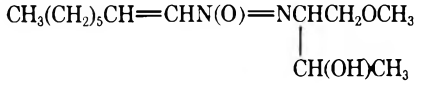
[a] Identified by comparison with an authentic sample, ref 5.

Table II. Bis Diazene *N*-Oxides[a]

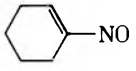
Product	Structure	Yield, %
10		75
11	$PhN(O)=N(CH_2)_4N=N(O)Ph$	46

[a] CuCl promoter.

formed nitroso olefins were unsuccessful since the precursors either polymerize readily, as does **14**,[10] or exist as stable dimeric azo dioxides, as does **15**[11] (insoluble). Attempted base-catalyzed dehydrohalogenation of both **6** and **12** yielded none of the desired *tert*-butylazoxyalkene, only intractable tars.



13



14

PhHC=CHNO

15

Mechanistic Considerations. The condensation of nitrosobenzene with *N,N*-dichloro-*tert*-butylamine to form **7** was chosen as the standard system for the mechanistic study. This compound is produced in poorer yield than many of the others, possibly owing to competing elimination of dichloro amine from *t*-$BuNCl_2$ to form isobutylene. It has been shown[12] that tertiary alkyl *N,N*-dichloro amines can undergo such a transformation in the presence of a variety of promoters, including cuprous chloride, triethylamine, potassium iodide, and ferrous chloride. In spite of this limitation, the synthesis of *tert*-butylazoxybenzene was chosen as the standard owing to the ease of estimation of the percent yields and the absence of competing reactions, other than the above-mentioned elimination. There is no possibility of dehydrohalogenation, as with a primary or secondary alkyl *N,N*-dichloro amine, or nucleophilic attack on the carbonyl function, as with *N,N*-dichlorourethane. Indeed, when *N,N*-dichlorourethane was stirred with CuCN under the usual reaction conditions, product was formed whose ir and NMR spectra indicated the presence of ethyl cyanoformate. A run with nitrosobenzene and *N,N*-dichloro-*n*-butylamine in the absence of promoter yielded only starting material.

The yields of **7** and **3** obtained with various promoters are

Table III. Effect on Diazene *N*-Oxide Yield of Variation in $X(RNX_2)^a$

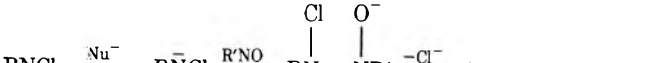
Compd	RN = N(O)R′: R	R′	Yield, %, when X = Cl	Br
7	*t*-Bu	Ph	44	90
6	*t*-Bu		38	69
3	CO_2Et	Ph	65	47
12	*t*-Bu	$(CH_3)_2CBr$		70

[a] CuCl promoter.

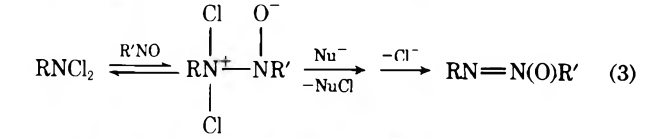
Table IV. Effect of Promoter on Diazene *N*-Oxide Yields

Promoter	Yield, % 7	3
Ag^0	57	
AgCl	11	
CuCl	49	65
$CuCl_2$	15	
CuCN	53	90
CuBr	53	
CuI	58	
Cu_2S	54	
$FeCl_2$	35	40
$FeSO_4$	~5	
CoBr	81	
$CoSO_4$	~2	
KI	79	
Et_3N	55	
NaCN	18	35
AgCN		68
$AgClO_4$		0
AgOAc		41

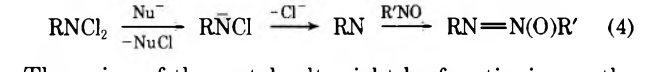
set forth in Tables IV–VI. The good results obtained with Et_3N, NaCN, and KI suggest nucleophilic attack on positive halogen in the *N,N*-dichloro amine, eq 2[13] or 3. Nucleophilic attack on the nitroso entity is known to occur.[14] As a mechanistic probe[15] for the validity of eq 2, the sodium salt of *N*-monochlorourethane, $(EtO_2CNCl)^-Na^+$, was allowed to react with nitrosobenzene in the absence of promoter. Formation of a complex mixture containing urethane and no more than 15–20% of **3** suggests that eq 2 does not represent a major pathway. Interpretation is difficult since some nitrene might be arising from the salt. A more likely possibility entails involvement of a nitrene,[5] eq 4. Nitrenes have previously been implicated as intermediates in various reactions entailing *N*-chloro compounds.[5,7,16]



(2)



(3)



(4)

The anion of the metal salt might be functioning as the nucleophile with the metal ion assuming the role of the Friedel–Crafts catalyst, either polarizing the nitroso bond or facilitating the removal of Cl^- in the last step. This conjecture is supported by the increase in yield of product **3** from AgCN vs. NaCN. Since nitroso compounds form stable complexes with certain metal ions,[17] such Lewis acid catalysis seems

Table V. Diazene *N*-Oxides from Ag°[a]

$C_6H_5N(O)=NR$		
Compd	R	Yield, %
7	*t*-Bu	60
2	C_6H_{11}	30
13[b]	*i*-Pr	17
1[b]	*n*-Bu	33

[a] $RNCl_2$:C_6H_5NO:Ag (Tollens') = 1:1:2 molar ratio, CH_3OH solvent. [b] See ref 5.

reasonable. In any event, in the absence of a reducing agent the presence of a nucleophile is necessary, as shown by the inability of $AgClO_4$ to promote the reaction.

The efficacy of silver metal, redox metal salts, and MgI_2/Mg as promoters suggests that a second reaction pathway is operative, namely a one-electron transfer from the reducing agent, eq 5. The nitrogen-centered radical then attacks the nitroso group to produce a nitroxide which yields product on loss of a chlorine atom. Freshly precipitated silver metal gives a substantial yield of product, in accord with published observations that *N*-chloro amines yield nitrogen radicals upon treatment with this reagent.[18] That the neutral silver is the promoter and not the generated silver chloride is shown by the small yield obtained with performed silver chloride. The superiority of cuprous chloride over cupric chloride lends credence to our contention since cuprous ion should be the weaker Lewis acid. The combination of MgI_2 and Mg, which presumably generates IMg, afforded **7** in 25% yield. Supporting this mechanism is the observation that radicals add to nitroso compounds yielding azoxy products,[19a] eq 6. Iodide ion, besides being a good nucleophile, is also a reducing agent, and may be playing both roles. Nucleophilic attack on positive chlorine would yield iodine monochloride which disproportionates to free iodine. Alternatively, the promoter may function as a one-electron reducing agent as in eq 5. There are examples[19b] of iodide reacting with dichloro amines to yield products best interpreted by means of a radical scheme. Although azo **16**, eq 7, could result from nitrene dimerization, peroxide **17** is more adequately accounted for on the basis of radical precursors, eq 8–10. The redox salts, ferrous sulfate and cobaltous sulfate, were also explored. Product resulted in both cases, but in very low yield. The insolubility of these salts in acetonitrile, or anion specificity,[20] could be a factor. Most of the data can be accommodated by a radical mechanism involving electron transfer reagents.

$$RNCl_2 + Ag^0 \xrightarrow{-AgCl} R\dot{N}Cl \xrightarrow{R'NO} RN(O\cdot)-NR'(Cl) \xrightarrow[-AgCl]{Ag^0} RN{=}N(O)R' \quad (5)$$

$$F_2N\text{-}C_6H_4\text{-}NO \xrightarrow{\cdot NF_2} F_2N\text{-}C_6H_4\text{-}N(O){=}NF \quad (6)$$

$$PhCH(R)NCl_2 \xrightarrow{I^-} PhCH(R)N{=}NCHR(Ph) \quad (7)$$

16

$$Ph_3CCl_2 \xrightarrow{I^-} Ph_3COOCPh_3 \quad (8)$$

17

$$Ph_3CNCl_2 \xrightarrow{I^-} Ph_3C\dot{N}Cl \xrightarrow{-NCl} Ph_3C\cdot \xrightarrow{O_2} \mathbf{17} \quad (9)$$

$$Ph_3CNCl_2 \xrightarrow[-NCl_2^-]{I^-} Ph_3C\cdot \xrightarrow{O_2} \mathbf{17} \quad (10)$$

In conclusion, the condensation of *N,N*-dihalo compounds with tertiary alkyl or aryl nitroso compounds can be effected with a wide variety of promoters, and probably can occur by several mechanistic pathways, depending on the promoter. The evidence suggests that reaction takes place initially by an ionic pathway, promoted by a nucleophile, or by a free-radical route, promoted by redox metal ions or neutral metals. Some flexibility in the choice of reaction conditions is thus possible. Hence, base-sensitive compounds can be prepared using a redox metal salt, and compounds sensitive to the presence of radicals or reducing agents can be synthesized using a nucleophile as promoter.

Table VI. Diazene *N*-Oxides from Silver Acetate

$C_6H_5N(O)=NR$		
Compd	R	Yield, %
7	*t*-Bu	42
2	C_6H_{11}	28
3	CO_2Et	55

Experimental Section

Infrared spectra were recorded on a Beckman IR-8 or a Perkin-Elmer 137 spectrophotometer. NMR spectra were taken on a Varian T-60A with tetramethylsilane as internal standard. Positive halogen content was determined by iodometric titration.[21] Melting and boiling points are uncorrected. Elemental analyses were performed by Baron Consulting Co., Orange, Conn.

***N,N*-Dimethylurea** was prepared by a published procedure.[22a]

***N,N*-Dichloro amines and amides** were prepared by a literature method.[23] After removal of solvent, the crude products were used without further purification.

Potassium salt of monochlorourethane (**18**) was prepared by a literature method.[24]

Trichloramine was prepared by a published procedure.[21] The methylene chloride solution was used without further purification.

***N,N*-Dibromo-*tert*-butylamine.** A solution of sodium hydroxide (30 g, 0.75 mol) and bromine (48 g, 0.3 mol) in water (150 ml) was stirred in an ice bath as *tert*-butylamine (15.3 g, 0.2 mol) in methylene chloride (200 ml) was added dropwise. The mixture was stirred for 5 h. The organic phase was removed, the aqueous phase was washed with methylene chloride, and the combined organic portion was dried over calcium chloride. Evaporation of solvent yielded product, red oil, 27 g (58%). Iodometric titration indicated the positive halogen content to be 100% of theory.

***N,N*-Dibromourethane.** A modified literature procedure was followed.[25] Silver acetate (25.1 g, 0.15 mol), suspended in carbon tetrachloride (400 ml), was stirred in an ice–salt bath as bromine (24 g, 0.15 mol) in carbon tetrachloride was added dropwise. After 10 min of stirring in the absence of light, urethane (4.5 g, 0.05 mol) was added and the mixture was stirred for 75 min at room temperature. The suspension was filtered, and evaporation of solvent yielded product, red oil (13.8 g, 100%). Iodometric titration indicated the positive halogen content to be 94% of theory.

1-Chloro-1-nitrosocyclohexane was prepared according to a published procedure.[26] The crude product was used.

***trans,trans*-1,4-Dichloro-1,4-dinitrosocylohexane** was prepared according to a literature method.[27]

2-Bromo-2-nitrosopropane was prepared according to a published procedure.[28] The undistilled product was used.

General Procedure for Diazene *N*-Oxides 1–13. The nitroso compound (0.01 mol) and the dihaloamino compound (0.01 mol) were stirred in acetonitrile (50 ml). In the synthesis of **9**, 0.005 mol of the tetrachlorodiamine was used. For **10**, trichloramine (0.01 mol) was added as a 0.7 M solution in methylene chloride. The promoter (0.01 mol of KI, Et_3N, AgCN, or NaCN; 0.02 mol of the others) was added and the mixture was stirred at room temperature overnight. In the cases of **5**, **10**, **11**, and **12**, the mixture was stirred at 0 °C for the first hour. The mixture was then poured into 500 ml of water. In the synthesis of **8**, the product was isolated by filtration. In the other cases, the water solution was extracted repeatedly with Et_2O. The combined extract was washed with H_2O, then with saturated aqueous NaCl, and dried over $CaCl_2$. Evaporation of solvent yielded the crude product as a brown oil. Compounds **8** and **9** were purified by crystallization. Products **1–6**, **11**, and **12** were chromatographed on silica gel with elution by benzene–petroleum ether (3:7). In the synthesis of **7** for the mechanistic studies, the crude product was held under reduced pressure at ca. 70 °C to remove unreacted *N,N*-dichloro-*tert*-butylamine, the only remaining impurity being nitrosobenzene. The percentage of product **7** in this mixture was estimated by comparison of

the integral of the *tert*-butyl singlet (δ 1.4) with the integral for the phenyl absorption (δ 8.2–7.0) in the NMR spectrum.

Tollens' Silver. Concentrated ammonia solution (about 50 ml) was added to a suspension of silver oxide[22b] (2.4 g) in water (30 ml) until the solid dissolved. Then 37% formaldehyde (40–50 ml) was added slowly with stirring and cooling in order to precipitate the silver metal. The solid was filtered and washed repeatedly with water, and then with methanol until free of formaldehyde.

7 from *t*-BuNCl$_2$–C$_6$H$_5$NO–Mg–MgI$_2$.[29] After a mixture of magnesium turnings (0.96 g, 0.013 mol) in 50 ml of tetrahydrofuran was warmed to 50 °C, iodine (1.68 g, 0.04 mol) was added in small amounts over a period of 1 h. The mixture slowly turned light brown in color. Then the mixture was cooled to room temperature and added to a solution of nitrosobenzene (1.07 g, 0.01 mol) and *N,N*-dichloro-*tert*-butylamine (1.44 g, 0.01 mol) in 50 ml of THF. The mixture became dark brown in color. Stirring was continued overnight. The mixture was then poured into 250 ml of water, and sodium thiosulfate (0.01 mol) was added until the color became lighter. The product was extracted into ether and dried over calcium chloride. Ether was removed by vacuum distillation and product was then distilled, bp 60–80 °C (0.5 mm), yield 25%. The properties (NMR, ir) of this fraction were identical with those of an authentic sample of **7**.

Characterization of Diazene *N*-Oxides. 1, 2, and **7** were identified by comparison with authentic samples.[5]

***N*-Ethylcarboxyl-*N'*-phenyldiazene *N'*-Oxide (3):** mp 37–38 °C; bp 112–114 °C (0.25 mm); NMR ($CDCl_3$) δ 1.37 (t, CH_3, 3.2 H), 4.42 (q, CH_2, 1.9 H), 7.50 (m, Ph, 3.0 H), 8.15 (m, Ph, 1.9 H); ir (neat) 1755 (C=O), 1490 (N=N), 1450 (NO), 1240 (C–O), 780, 695 cm^{-1} (Ph).

Anal. Calcd for $C_9H_{10}N_2O_3$: C, 55.65; H, 5.19; N, 14.43. Found: C, 55.38; H, 5.05; N, 14.49.

***N*-Benzoyl-*N'*-phenyldiazene *N'*-Oxide (4):** mp 50–52 °C; NMR ($CDCl_3$) δ 8.20 (m, Ph, 2.24 H), 7.94 (m, Ph, 1.9 H), 7.50 (m, Ph, 5.9 H); ir (neat) 1700 (C=O), 1580 (Ph), 1470 (N=N), 1430 (NO), 1230, 1320 (C–N), 781, 690 cm^{-1} (Ph).

Anal. Calcd for $C_{13}H_{10}N_2O_2$: C, 69.00; H, 4.46; N, 12.39. Found: C, 68.97; H, 4.66; N, 12.64.

***N*-Dimethylcarbamyl-*N'*-phenyldiazene *N'*-Oxide (5):** mp 44–46 °C; NMR ($CDCl_3$) δ 8.18 (m, Ph, 2.0 H), 7.53 (m, Ph, 3.4 H), 3.06 (s, CH_3, 2.7 H), 2.87 (s, CH_3, 3.0 H); ir (neat) 1680 (C=O), 1480 (N=N), 1430 (NO), 1370 (CH_3), 791, 695 cm^{-1} (Ph).

Anal. Calcd for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 55.70; H, 5.52; N, 21.83.

***N*-*tert*-Butyl-*N'*-chlorocyclohexyldiazene *N'*-Oxide (6):** bp 53–54 °C (0.25 mm); NMR ($CDCl_3$) δ 1.0–2.8 (m, aliphatic), 1.30 (s, C_4H_9); ir (neat) 1490 (N=N), 1440 (NO), 1350 cm^{-1} (*t*-C_4H_9).

Anal. Calcd for $C_{10}H_{19}N_2OCl$: C, 54.91; H, 8.76; N, 12.81; Cl, 16.21. Found: C, 55.17; H, 8.93; N, 13.01; Cl, 16.45.

1,4-Dichloro-1,4-bis(*N*-ethylcarboxylazo)cyclohexane *N',N'*-Dioxide (10): mp 136–139 °C; NMR ($CDCl_3$) δ 4.08 (q, OCH_2, 3.9 H), 2.77 (s, CCH_2, 7.8 H), 1.40 (t, CH_3, 6.3 H); ir ($CHCl_3$) 1750 (C=O), 1500 (N=N), 1450 (NO), 1200 cm^{-1} (CO).

Anal. Calcd for $C_{12}H_{18}O_6N_4Cl_2$: C, 37.42; H, 4.71; N, 14.55; Cl, 18.41. Found: C, 37.67; H, 4.69; N, 14.74; Cl, 18.69.

1,2-Bis(*N*-phenylazo)ethane *N',N'*-Dioxide (11): mp 155–156 °C; NMR ($CDCl_3$) δ 8.14 (m, Ph, 3.7 H), 7.13 (m, Ph, 6.9 H), 4.18 (s, CH_2, 3.4 H); ir (Nujol) 1470 (N=N), 1430 (NO), 790, 690 cm^{-1} (Ph).

Anal. Calcd for $C_{14}H_{14}N_4O_2$: C, 62.2; H, 5.2; N, 20.7. Found: C, 61.9; H, 5.3; N, 20.7.

***N*-Phenyl-*N'*-chlorodiazene *N*-Oxide (8):** bp 68–70 °C (0.6 mm) [lit.[6] bp 57 °C (0.5 mm)]; NMR[30] (CCl_4) δ 7.2–8.2 (m, Ph); ir (neat) 1475 (N=N), 1430 cm^{-1} (NO); mass spectrum *m/e* (rel intensity) 156 (51) (M^+), 112 (73) ($M^+ - N_2O$), 107 (100) (M^+ – NCl).

Anal. Calcd for $C_6H_5ClN_2O$: C, 46.03; H, 3.22; N, 17.89. Found: C, 45.92; H, 3.40; N, 17.82.

***N*-Benzoyl-*N'*-*tert*-butyldiazene *N'*-Oxide (9):** mp 43–45 °C; NMR ($CDCl_3$) δ 7.84 (m, Ph, 1.8 H), 7.53 (m, Ph, 3.1 H), 1.68 (s, *t*-C_4H_9, 9.1 H); ir ($CHCl_3$) 1720 (C=O), 1600 (Ph), 1480 (N=N), 1450 cm^{-1} (NO).

Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.05; H, 6.86; N, 13.58. Found: C, 64.06; H, 6.80; N, 13.41.

***N*-*tert*-Butyl-*N'*-bromoisopropyldiazene *N'*-Oxide (12):** bp 96–99 °C (50 mm); NMR (CCl_4) δ 2.15 (s, $CBrCH_3$, 6.1 H), 1.30 (s, *t*-C_4H_9, 8.9 H); ir (neat) 1490 (N=N), 1450 (NO), 1360 cm^{-1} (*t*-C_4H_9).

Anal. Calcd for $C_7H_{15}N_2OBr$: C, 37.68; H, 6.78; N, 12.56; Br, 35.81. Found: C, 37.40; H, 6.65; N, 12.32; Br, 36.11.

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Registry No.—**3,** 56751-20-3; **4,** 56751-21-4; **5,** 56751-22-5; **6,** 58426-22-5; **7,** 52123-67-8; **8,** 40946-24-5; **9,** 58426-23-6; **10,** 58426-24-7; **11,** 58438-07-6; **12,** 58426-25-8; *N,N*-dimethylurea, 598-94-7; monochlorourethane K salt, 16844-21-6; trichloramine, 10025-85-1; *N,N*-dibromo-*tert*-butylamine, 51655-36-8; *N,N*-dibromourethane, 51066-06-9; 1-chloro-1-nitrosocyclohexane, 695-64-7; *trans-trans*-1,4-dichloro-1,4-dinitrosocyclohexane, 58426-26-9; 2-bromo-2-nitrosopropane, 7119-91-7; nitrosobenzene, 586-96-9; *N,N*-dichloro-*tert*-butylamine, 2156-72-1.

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(30) Essentially identical with that of authentic material.[6] We thank Professor le Noble for the spectral data.

Conversion of Conjugated p-Tosylhydrazones to the Corresponding Ethers by Sodium Borohydride, Sodium Alkoxide, or Potassium Carbonate in Alcohol Solvents

Romano Grandi, Alessandro Marchesini, Ugo M. Pagnoni,* and Roberto Trave

Istituto di Chimica Organica, Università di Modena, 41100 Modena, Italy

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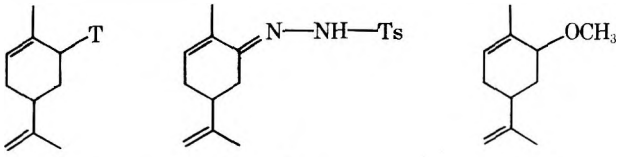
p-Tosylhydrazones of conjugated (olefinic or aromatic) carbonyl compounds undergo with $NaBH_4$ in methanol an elimination process in preference to reduction, thereby providing methyl ethers instead of hydrocarbons. The combination of base ($NaBH_4$, NaOR, or K_2CO_3) and alcohol provides an effective and convenient system for the transformation of these conjugatively deactivated derivatives into the corresponding ethers, mostly without allylic rearrangement. The sequence tosylhydrazone → diazoalkene (aryldiazomethane) → diazonium–alkoxide ion pair → ether is suggested as the most suitable mechanistic description.

The reduction of p-tosylhydrazones with $NaBH_4$ in methanol or in aprotic solvents (such as THF or dioxane) gives saturated hydrocarbons in high yields under mild conditions.[1-3] The mechanism of this reaction apparently involves[2,4,5] initial chelation of the tosylhydrazone by a Lewis acid followed by reduction to an intermediate tosylhydrazine (or its organometallic equivalent), and subsequent thermal decomposition.

A need for [6-^{3}H]limonene (1) for biogenetic studies prompted application of this reaction to the reduction of carvone p-tosylhydrazone[6] (2).



1 2 3

Treatment of 2 with $NaBH_4$ in MeOH[1] gave, instead of the expected limonene (1), a high yield of carveyl methyl ether (3) as a mixture of stereoisomers. The corresponding reaction in dioxane was extremely slow, giving only traces of 1 after 48 h. This unexpected result led us to examine the behavior of other α,β-unsaturated and also aromatic carbonyl derivatives in this reaction.

As seen in Table I, the reaction in MeOH[10] afforded the corresponding methyl ethers in satisfactory yields for all the p-tosylhydrazones studied. However, in dioxane the yields of hydrocarbons were much lower for conjugated derivatives than for saturated examples,[1,2] under identical experimental conditions.

The results outlined in Table I demonstrate that, as with α,β-unsaturated carbonyls in the presence of nucleophilic reagents, the reactivity of the carbon–nitrogen double bond toward hydride is drastically reduced.[8a,b] The virtually quantitative recovery of the tosylhydrazones and absence of alkyltosylhydrazines in the reactions performed in dioxane indicate that the step which is blocked is the addition of hydride and not the subsequent decompositon of alkyltosylhydrazine.

From this it follows that, in methanol, the lower reactivity of the carbon–nitrogen double bond coupled with the protic and nucleophilic nature of the solvent and the alkalinity of the medium favor alkaline cleavage[11,12] analogous to the Bamford–Stevens reaction.[13] This view is strongly supported by the successful conversions of the conjugated p-tosylhydrazones with MeONa[14] or K_2CO_3 and methanol (Table I). The reactions effected by base in methanol may involve (Scheme I) the decomposition of the tosylhydrazone anion to an intermediate diazo derivative (as generally accepted for the Bamford–Stevens reaction). This is supported by the appearance, in the tests carried out on aromatic substrates, of a transient light-orange color. The formation of these diazo derivatives is more evident when working with MeONa in methanol; in fact, under these conditions the diazo derivatives can be isolated.[13,15,16] Although in the case of olefinic tosylhydrazones the presence of diazo derivatives in appreciable quantities could not be demonstrated,[17] we believe that they are formed during the first stage of the reaction, but, being less stable than aryldiazomethanes, evolve to final products at a much faster rate.

The reaction of 1-oxoalkanephosphonate p-tosylhydrazones with $NaBH_4$[18] is apparently intermediate between p-tosylhydrazones of saturated carbonyls and those in the present study. When working in THF, the former derivatives afford the corresponding products of normal reduction in high yield (65–72%), while in methanol the corresponding diazo derivatives are isolated (85–90%), resulting from a thermal decomposition of the tosylhydrazone anion.

Even if the possibility of competing thermal[19] reactions (path b) cannot be excluded, the protic reaction medium and the mild conditions employed in this study suggest that the diazo derivative reacts[20,21] with a weakly acidic proton donor, such as the hydroxyl solvent, to form a diazonium ion[22] followed by N_2 elimination to a carbonium ion (path a). In fact, vinyldiazoalkanes, which are less stable than their aromatic counterparts and thus more easily protonated,[20] cannot be detected in the reaction medium. Further, the reaction of phenyldiazomethane with methanol was much faster in the absence of MeONa, resulting in virtually immediate disap-

Scheme I

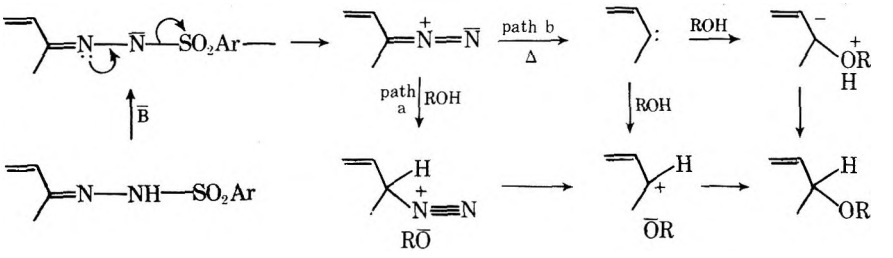
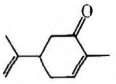
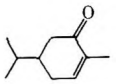
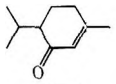
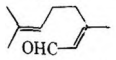
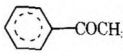
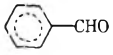


Table I. Conversion[a] of Conjugated *p*-Tosylhydrazones to Allylic (or Benzylic) Methyl Ethers

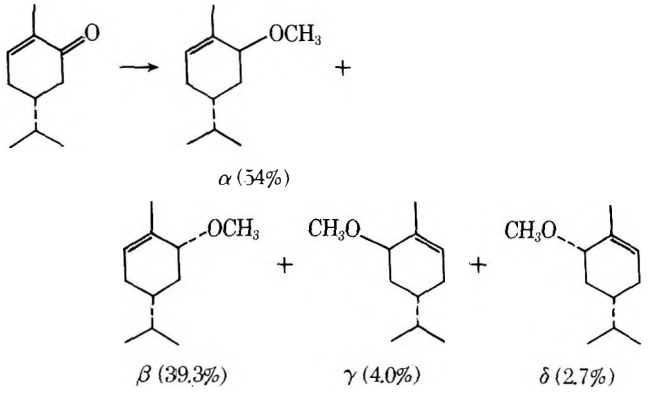
Registry no.	*p*-Tosylhydrazone[n] of	Mp, °C	$NaBH_4$ MeOH	(h)	$NaBH_4$ Dioxane	(h)	MeONa MeOH	(h)	K_2CO_3 MeOH	(h)
21195-60-8		156–157	77 [0.5][b]	(48)	[8.5][b]	(48)	69[c]	(48)	67	(48)
58548-70-2		137–138	86 [0.9][b]	(30)	[19][b]	(72)	80	(48)	70	(48)
21195-62-0		144–145[d]	80 [0.7][b]	(48)	st. m.	(72)	73	(48)	61	(48)
58580-63-5		125–127	67 [1.4][b]	(48)	[5.2][b]	(48)	56	(48)	54	(48)
58548-71-3			73[e,f] [0.7][b]	(40)			60[e,f]	(40)	69[e,f]	(40)
21301-41-7	Cholest-4-en-3-one	105–106	26	(48)	st. m.	(48)	19	(48)	16	(48)
4545-21-5		146–147[g]	69[h] [1][b]	(48)	st. m.	(48)	58	(48)	54	(48)
17336-59-3		177–179	74 [5][b,i,l]	(24)	[15][b,i]	(24)	70	(24)	76	(24)
1666-17-7		128–129[m]	64 [3][b]	(24)	[16][b]	(24)	60[c]	(24)	69	(24)

[a] Overall yields were determined by isolation and do not take into account recovered starting material. [b] Yields of allylic (benzylic) hydrocarbons. [c] Use of EtONa in ethanol and of *i*-PrONa in 2-propanol afforded the corresponding ethers (see Experimental Section). [d] Lit.[8b] 143.5–145 °C. [e] Tosylhydrazone not isolated. [f] Product consisted of a mixture (~7:3) of neryl and linalyl methyl ether. [g] Lit.[16] 147.5–150 °C. [h] Use of ethanol afforded the corresponding ethyl ether in 47% yield (see Experimental Section). [i] Mixture of hydronaphthalenes. [l] The amount of tetralin slowly increases with excess $NaBH_4$. The yields of 30% reported by Caglioti[2] is possibly due to a misleading computation of the gas chromatographic peak (L. Caglioti, private communication). [m] Lit.[8b] 128.5–130 °C. [n] All isolated *p*-tosylhydrazones gave satisfactory elemental analyses (±0.3% for C, H, N) the results of which have been provided to the Editor.

pearance of the diazo compound and excellent yields of ether; this strongly indicates an acid-catalyzed reaction of the diazo compound. A short-lived diazonium ion will then lead to the formation of a stable allylic or benzylic carbonium ion.

The nucleophile employed showed differing behavior with the aromatic systems than with the olefinic cases; this is probably due to the different stability of the carbocation. Thus, the *p*-tosylhydrazone of benzaldehyde exhibited a progressive reduction of reactivity (7:5:1, relative final yields) in parallel tests carried out with 0.05 M solutions of MeONa in methanol, EtONa in ethanol, and *i*-PrONa in 2-propanol, while the carvone derivative (2) exhibited almost identical reactivities with the three systems.

The analysis of the mixture of isomeric carvotanacetyl methyl ethers[23] obtained both with $NaBH_4$ and MeONa in methanol is of interest and is presented below.



The simplest explanation for the very small quantities of isomers resulting from allylic rearrangement (γ and δ) is that a diazonium–methoxide ion pair is formed which loses nitrogen unimolecularly without dissociation; the predominance of trans over cis isomers can best be explained by steric hindrance.

The mild reaction conditions and the satisfactory yields obtained in the reaction of conjugated *p*-tosylhydrazones with alcohols in basic medium suggest the latter as an attractive alternative to that in which the corresponding allylic and benzylic ethers are obtained from unsaturated ketones by means of initial reduction followed by ether formation.

The scope and applications of the reactions are currently in progress.

Experimental Section

Ir spectra were determined with a Perkin-Elmer 257 instrument. NMR spectra were measured on a JEOL C-60 instrument, with Me_4Si as internal standard; chemical shifts have been recorded in δ values. Mass spectra were determined with a Varian MAT 112 spectrometer. Optical rotations were measured on a Perkin-Elmer 141 instrument. Microanalyses were performed by Istituto di Chimica Generale, University of Modena.

All the conjugated ethers were compared (GLC, ir, and NMR) with authentic samples obtained commercially or prepared by standard procedures, usually[23] from the corresponding carbonyl compound by hydride reduction and subsequent methylation (NaH/CH_3I). The allylic hydrocarbons were identified on GC–MS by comparison with samples obtained commercially or prepared from the alcohol by mesylation followed by hydride reduction.

***p*-Tosylhydrazone Formation. General Procedure.** The *p*-tosylhydrazones were readily prepared in good yield by addition of *p*-tosylhydrazine (10% molar excess) to a solution of the carbonyl

compound in methanol followed by refluxing for 0.5–5 h. In all cases the products were identified through elemental analyses (which were made available to the Editor and which were well within the limits of acceptable error) and infrared and NMR spectra, which are available on request. The materials were pure enough for use in the reactions.

General Decomposition Procedures. A. With $NaBH_4$ in Methanol. To a stirred solution of 3 mmol of the tosylhydrazone in 35–50 ml of methanol was added $NaBH_4$ (45 mmol) in small portions during 1.5 h. The solution was then refluxed for the appropriate length of time (Table I), the reaction being monitored by TLC and GLC. Water was then added, and the mixture was extracted with ether (or methylene chloride in the case of the steroid) (3 × 25 ml); the organic solution was then washed with water, dried (Na_2SO_4), and concentrated. The residue was analyzed by GLC on a 4-m 5% WEAS column and on a 2-m 5% SE-30 column and the products were fractionated by using a silica gel column (*n*-hexane–ether gradient) and purified by distillation.

B. With MeONa in Methanol. Reaction mixtures made 0.045 M in the tosylhydrazone and 0.05 M in MeONa in methanol were refluxed for the appropriate length of time (Table I). Water was then added and the above workup employed to obtain the reaction products.

C. With K_2CO_3 in Methanol. The procedure was identical, except that the solution was 0.06 M in anhydrous K_2CO_3.

Reduction with $NaBH_4$ in Dioxane. The general procedure was that described by Caglioti.[1] The products were recovered in ether which was distilled at 1 atm pressure to give a residue which was analyzed by GC–MS in comparison with authentic samples.

Carveyl Methyl Ethers. The isomer mixture was analyzed on GC–MS in comparison with samples prepared[23] from the *cis*- and *trans*-carveol by NaH/CH_3I in THF: $[\alpha]^{20}D$ −69.5° (*c* 2.1, MeOH) from $NaBH_4$/MeOH, −66.7° (*c* 2.0, MeOH) from MeONa/MeOH and −68.1° (*c* 2.1, MeOH) from K_2CO_3/MeOH; NMR ($CDCl_3$) δ, 1.7 (6 H, br s, CH_3C=), 3.32 and 3.37 (3 H, two s, CH_3O), 3.45 (1 H, m, CHO), 4.72 (2 H, s, CH_2=C), and 5.57 (1 H, m, CH=C).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.63; H, 10.75.

Carveyl Ethyl Ethers. They were obtained as an isomer mixture (GC–MS), in 65% yield by 0.05 M EtONa in ethanol, following the general procedure (at 68 °C for 48 h): NMR (CCl_4) δ 1.2 (3 H, t, CH_3C), 1.77 (6 H, br s, CH_3C=); 3.52 (2 H, q, CH_2O), 3.76 (1 H, m, CHO), 4.78 (2 H, br s, CH_2=C), and 5.53 (1 H, br t, CH=C).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.95; H, 11.03.

Carveyl Isopropyl Ethers. They were obtained as an isomer mixture (GC–MS), in 62% yield by 0.05M *i*-PrONa in 2-propanol following the general procedure (at 68 °C for 48 h): NMR (CCl_4) δ 1.13 (6 H, d, CH_3C), 1.70, 1.72, and 1.74 (6 H, three s, CH_3C=), 3.5–4.0 (2 H, m, CHO), 4.73 (2 H, br s, CH_2=C), and 5.5 (1 H, m, CH=C).

Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.47; H, 11.58.

Carvotanacetyl Methyl Ethers. The cis and trans (1:1.4, GLC) isomers were separated by repeated column chromatography over silica gel using a *n*-hexane–benzene gradient and purified by distillation.

Cis isomer: $[\alpha]^{20}D$ −76.9° (*c* 2.05, MeOH).

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.54; H, 12.07.

Trans isomer: $[\alpha]^{20}D$ −71.4° (c 2.1, MeOH).

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.39; H, 11.93.

The ir and NMR spectra were identical with those previously obtained.[23]

Isophoryl Methyl Ether. The product was purified by distillation (82–83 °C (14 mm): NMR ($CDCl_3$) δ 0.88 and 0.98 (3 H each, s, CH_3C), 1.71 (3 H, br s, CH_3C=), 3.37 (3 H, s, CH_3O); 3.8 (1 H, m, CHO), and 5.52 (1 H, br s, CH=C). Its GLC retention time, ir, and NMR spectra were superimposable with those of a sample prepared according to the literature.[24]

Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 78.13; H, 11.90.

Piperityl Methyl Ether. The reaction mixtures consisted of two methyl ethers (~1:1, GLC), which showed (GC–MS) the same molecular ion (M^+ *m/e* 168) and identical fragmentation pattern. They were separated by preparative GLC (10% QF1, 100 °C) and purified by distillation, bp 90–93 °C (15 mm). NMR ($CDCl_3$) of the isomer with lower retention time showed signals at δ 0.93 [6 H, d (*J* = 6 Hz), CH_3C], 1.72 (3 H, br s, CH_3C=), 3.33 (3 H, s, CH_3O), 3.62 (1 H, m, CHO), and 5.70 (1 H, m, CH=C).

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.56; H, 12.24.

NMR ($CDCl_3$) of the other isomer had signals at δ 0.85 and 0.95 [3 H each, d (*J* = 6 Hz), CH_3C], 1.68 (3 H, br s, CH_3C=), 3.30 (3 H, s, CH_3O), 3.62 (1 H, m, CHO), and 5.48 (1 H, br s, CH=C).

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.80; H, 11.75.

The NMR spectra and ir absorptions were identical with those of the two epimeric methyl ethers (1:3, GLC) obtained from piperitone by the procedure above indicated.

Neryl and 1,5-Dimethyl-1-vinyl-4-hexenyl Methyl Ethers. The two methyl ethers (~7:3, GLC) were separated by chromatography over silica gel, eluting with a *n*-hexane–benzene gradient, and purified by distillation. **Neryl methyl ether:** NMR (CCl_4) δ 1.62 (3 H, s, CH_3C=), 1.68 (6 H, s, CH_3C=), 3.31 (3 H, s, CH_3O), 3.98 [2 H, d (*J* = 6.5 Hz), CH_2O], 5.1 (1 H, m, CH=C), and 5.4 (1 H, br t, CH=C).

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.83; H, 11.81.

1,5-Dimethyl-1-vinyl-4-hexenyl methyl ether: NMR (CCl_4) δ 1.2 (3 H, s, CH_3C), 1.62 and 1.69 (3 H each, br s, CH_3C=), 3.11 (3 H, s, CH_3O), 4.9–5.3 (3 H, m, CH_2=C), and 5.5–6.1 (1 H, m, CH=C).

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.68; H, 11.74.

Cholesteryl Methyl Ether. The mixture (GLC) of 3β and 3α derivative was not separated, but purified by distillation: bp 181–185 °C (0.01 mm); NMR ($CDCl_3$) δ 3.35 and 3.38 (3 H, two s, CH_3O), 3.4–3.9 (1 H, m, CHO), and 5.4 (1 H, m, CH=C).

Anal. Calcd for $C_{28}H_{48}O$: C, 83.93; H, 12.08. Found: C, 83.68; H, 12.30.

(α-Phenyl)ethyl Methyl Ether: NMR ($CDCl_3$) δ 1.37 [3 H, d (*J* = 6 Hz), CH_3C], 3.12 (3 H, s, CH_3O), 4.21 (1 H, q, CHO), and 7.17 (5 H, br s, phenyl).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.50; H, 8.72.

(α-Phenyl)ethyl Ethyl Ether. When the $NaBH_4$ decomposition was carried out in ethanol according to the general procedure the ethyl ether was obtained in 47% yield; no allylic hydrocarbon was detected in the product mixture. NMR ($CDCl_3$) δ 1.2 (3 H, t, CH_3C), 1.46 [3 H, d (*J* = 6 Hz), CH_3C], 3.37 (2 H, q, CH_2C), 4.41 (1 H, q, CHO), and 7.23 (5 H, br s, phenyl).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 80.06; H, 9.40.

α-Tetrahydronaphthalenyl Methyl Ether. The methyl ether was separated from the hydrocarbons by column chromatography on silica gel eluting with a *n*-hexane–ether gradient: NMR ($CDCl_3$) δ 1.7–2.2 (4 H, m, CH_2C), 2.8 (2 H, m, CH_2Ar); 3.42 (3 H, s, CH_3O), 4.32 (1 H, t, CHO), and 7.0–7.5 (4 H, m, aromatic).

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.60; H, 8.73.

1,2-Dihydronaphthalene: NMR ($CDCl_3$) δ 2.4 (2 H, m, CH_2C=), 2.8 (2 H, m, CH_2Ar), 6.08 (1 H, m, CH=C), 6.5 [1 H, d (*J* = 9 Hz), CH=C], and 7.08 (4 H, br s, aromatic).

Tetralin: NMR ($CDCl_3$) δ 1.79 (4 H, m, CH_2C), 2.78 (4 H, m, CH_2Ar) and 7.08 (4 H, s, aromatic).

Benzyl Methyl Ether: NMR (CCl_4) δ 3.3 (3 H, s, CH_3O), 4.38 (2 H, s, CH_2O), and 7.27 (5 H, s, phenyl).

Anal. Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.82; H, 8.30.

Benzyl Ethyl Ether. It was obtained by 0.05 M EtONa in ethanol following the general procedure (at 68 °C for 24 h), in 43% yield: NMR (CCl_4) δ 1.18 (3 H, t, CH_3C), 3.46 (2 H, q, CH_2O), 4.40 (2 H, s, CH_2O), and 7.27 (5 H, s, phenyl).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.42; H, 9.02.

Acknowledgment. We gratefully acknowledge support of this work by the Consiglio Nazionale delle Ricerche, Rome.

Registry No.—*cis*-Carveyl ethyl ether, 58580-64-6; *trans*-carveyl ethyl ether, 58580-65-7; *cis*-carveyl isopropyl ether, 58548-72-4; *trans*-carveyl isopropyl ether, 58548-73-5; *cis*-carvotanacetyl methyl ether, 55449-15-5; *trans*-carvotanacetyl methyl ether, 55378-54-6; isophoryl methyl ether, 50987-46-7; *cis*-piperityl methyl ether, 58548-74-6; *trans*-piperityl methyl ether, 58548-75-7; neryl methyl ether, 2565-83-5; 3β-cholesteryl methyl ether, 1981-91-5; 3α-cholesteryl methyl ether, 17320-23-9; (α-phenyl)ethyl methyl ether, 4013-34-7; (α-phenyl)ethyl ethyl ether, 3299-05-6; α-tetrahydronaphthaleneyl methyl ether, 1008-18-0; 1,2-dihydronaphthalene, 447-53-0; tetralin, 119-64-2; benzyl methyl ether, 538-86-3; benzyl ethyl ether, 539-30-0; 1,5-dimethyl-1-vinyl-4-hexenyl methyl ether, 2565-82-4.

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On the Mechanism of the Thermal *N*-Nitropyrazole Rearrangement. Evidence for a [1,5] Sigmatropic Nitro Migration[1]

Joseph W. A. M. Janssen, Clarisse L. Habraken, and Robert Louw*

Gorlaeus Laboratories, University of Leiden, Leiden, The Netherlands

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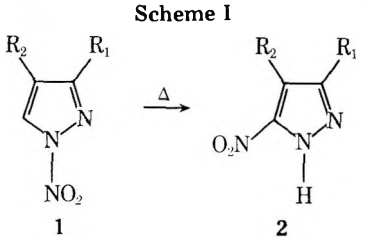
The title reaction, which smoothly proceeds at ca. 150 °C, displays first-order kinetics and is affected neither by acids or bases, nor scavengers for free radicals or for NO_2^+. Our kinetic studies further showed that replacement of 3(5)H by D has no effect on the rate of this intramolecular process. Solvent effects are surprisingly small. Substituents at the 3, 4, or 5 position exert only modest influence on rates and activation parameters; $\Delta H^{\ddagger}$ values are in the range 30–36 kcal mol^{-1}, $\Delta S^{\ddagger}$ being 2 ± 5 eu. The reaction, which can also be performed in the vapor phase, apparently does not proceed heterolytically; the type of solvent effect points to a transition state which is somewhat less polar than the starting compound. Isomerizations in benzene lead to trace amounts only of the corresponding (1−) phenylpyrazoles. The N–NO_2 bond strength is estimated to be 45–50 kcal mol^{-1}. Hence, a homolytic mechanism involving free (1−) pyrazolyl radicals is highly unlikely. All experimental data are compatible with a rate-determining [1,5] shift of NO_2 to give a 3*H*-pyrazole as an intermediate, which subsequently isomerizes into the 3(5)-nitropyrazole. The first step is discussed in some detail. As the reverse reaction could not be observed, the overall process is markedly exothermal. With 4-substituted 1-nitropyrazoles some denitration (apparently caused by steric hindrance) is competing with rearrangement.

Thermal rearrangement of *N*-nitropyrazoles unsubstituted at the 5 position (**1**) has been proven to be a convenient method for the preparation of 3(5)-nitropyrazoles (**2**)[2,3] (Scheme I). The isomerizations can be performed at moderate temperatures (120–190 °C) in various solvents. Normally, the 3(5)-nitropyrazoles are formed quantitatively; in some instances side reactions, particularly denitration, are observed.

Thermal N → C migration of NO_2 is not restricted to pyrazoles; analogous migrations were found in *N*-nitroindazoles,[4] triazoles,[5] and imidazoles.[6]

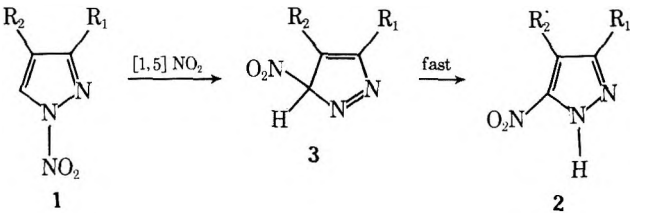
Scheme I



1 **2**

a, $R_1 = R_2 = H$
b, $R_1 = CH_3$; $R_2 = H$
c, $R_1 = C(CH_3)_3$; $R_2 = H$
d, $R_1 = C_6H_5$; $R_2 = H$
e, $R_1 = p\text{-}NO_2C_6H_5$; $R_2 = H$
f, $R_1 = NO_2$; $R_2 = H$
g, $R_1 = H$; $R_2 = CH_3$
h, $R_1 = H$; $R_2 = C_2H_5$

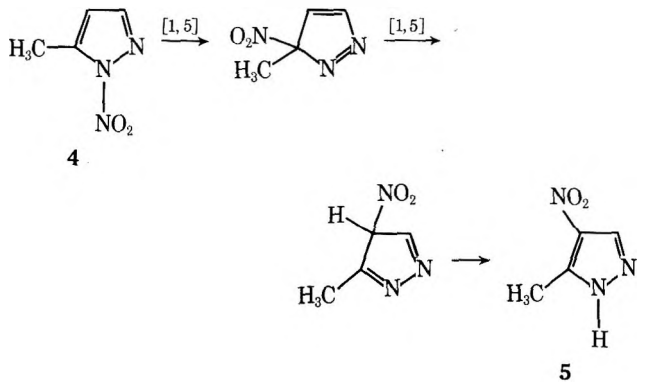
Scheme II



1 **3** **2**

For the mechanism of the rearrangement of *N*-nitro(pyr)-azoles, a two-step process has been proposed,[3,5] involving an unprecedented [1,5] sigmatropic shift of the nitro group and fast rearomatization of the intermediately formed 3*H*-pyrazole (**3**) (Scheme II). For thermal N → C migrations of alkenyl groups in pyrroles and, recently, imidazoles, similar mechanisms have been suggested.[7,8] Our proposition was based on the apparent intramolecularity of the *N*-nitropyrazole rearrangement. The isomerization obeys first-order kinetics perfectly and no divergent reaction paths were observed when the thermolyses were performed in the presence of reagents (e.g., phenol, quinoline, and toluene) which may act as catalyst or scavenger of intermediates (see ref 2). Moreover, a sigmatropic process adequately accounts for NO_2 migration to the 5(3) position. Migration to the 4 position has only been ob-

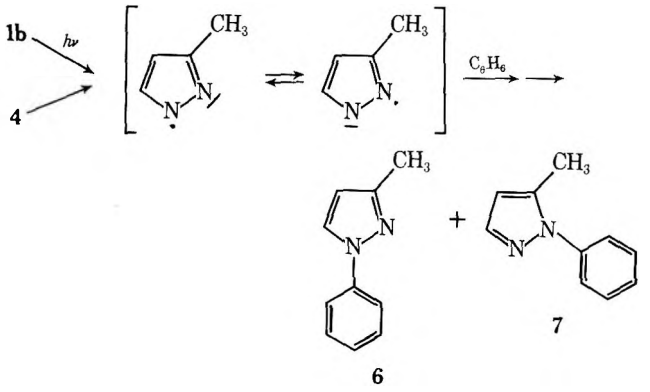
Scheme III



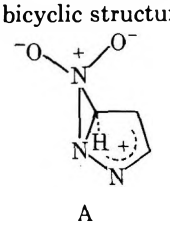
served[2,3] with a 5-substituted 1-nitropyrazole: 5-methyl-1-nitropyrazole (**4**) gives 3(5)-methyl-4-nitropyrazole (**5**) as major product. In this case, formation of a 4-nitropyrazole can be explained by assuming two sequential [1,5] nitro shifts (Scheme III). Formation of a small amount of the 5(3)-nitro isomer **2b** on thermolysis of **4** is the result of a noteworthy side reaction: slow isomerization into the less strained *N*-nitro compound **1b**, followed by rearrangement to **2b**.[2]

In itself, the differing behavior of 3- and 5-methyl substituted 1-nitropyrazoles excludes a common intermediate. Hence dissociation, viz., initial homo- or heterolysis of the N–NO_2 bond, is not involved, as in these cases the resulting pyrazolyl fragments (radical or anion) should give rise to the same (ratio of) products. Recently we showed that *N*-pyrazolyl radicals generated from 3- and 5-methyl substituted pyrazole precursors are, at least at room temperature, indistinguishable.[9] Thus, *photolysis* of *N*-nitropyrazoles **1b** and **4** in benzene leads to the same products, viz., isomeric *N*-phenylpyrazoles **6** and **7**, in a 4:1 ratio; apparently these derivatives arose via homolytic aromatic substitution (Scheme IV).

Scheme IV



Although the thermally induced, intramolecular rearrangement of *N*-nitropyrazoles obviously proceeds with a high degree of selectivity, more data are needed to define the transition state(s) involved in the NO_2 shift. Information on other, possibly sigmatropic, NO_2 shifts is very scarce,[10] and on the basis of the available data processes involving tight (caged) radical[11] or ion pairs cannot be excluded rigorously. Another possibility is that of migration via a reactive intermediate, particularly bicyclic structure A. For the thermal



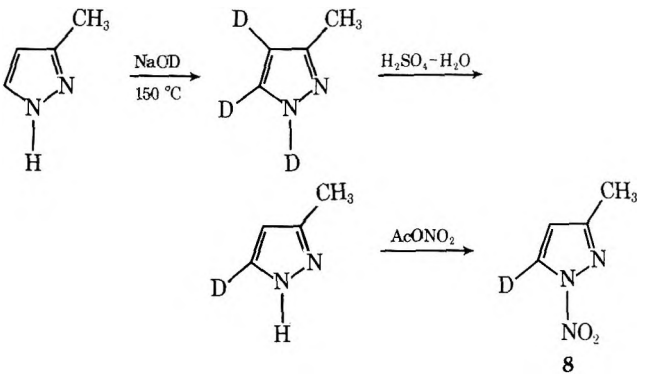
A

rearrangements of 3*H*-pyrazoles into N-substituted pyrazoles (van Alphen rearrangements,[12] the migrating groups being, e.g., cyano or acyl), analogous bicyclic intermediates have been proposed,[13] although most authors favor a sigmatropic mechanism.[14]

A way to discriminate between these possible modes of NO_2 migration might be determination of activation parameters. However, then first the possibility of tautomerization **3** → **2** (see Scheme II) being rate determining has to be eliminated. Note that intermediate **3** is a 3*H*-pyrazole, and these compounds can only be isolated when the 3 position is disubstituted.[15] Thus tautomerization **3** → **2**, which can be either a [1,5] hydrogen shift or a solvent-assisted proton transfer, is probably faster than remigration of the nitro group. Kinetic parameters for the overall reaction then bear upon the first step(s). Alternatively, if remigration of NO_2 is faster than tautomerization, introduction of D at the 5 position should give rise to a primary kinetic H/D isotope effect.

5-Deuterio-3-methyl-1-nitropyrazole (**8**) was prepared according to Scheme V (cf. ref 16 and 3). A competition experiment with the nondeuterated derivative **1b** at 140 °C (hexachloroacetone solution, isomerization followed by NMR, see Experimental Section) did not reveal a primary isotope effect: $k_H/k_D = 1.0 \pm 0.1$. Hence, hydrogen migration is not involved in the rate-determining step(s).

Scheme V



Results and Discussion

Kinetic Measurements. First, the solvent effect on the rearrangement of a representative *N*-nitropyrazole was studied. The isomerization rate of the 3-methyl derivative **1b** at 140 °C was measured in six solvents of differing polarity (see Table I). Kinetic data are based on the decay of *N*-nitropyrazole, followed by GLC. TLC analysis after completion of the reactions revealed that in all solvents studied the expected product **2b** was formed without detectable amounts of side products.[17] In all solvents, first-order kinetics was observed.

In three solvents of markedly different character (*n*-decane, nitrobenzene, and propylene glycol), rate constants were determined at different temperatures, and from the Arrhenius plots obtained the activation parameters were calculated. The results, together with rate constants at 140 °C in the different solvents, are listed in Table I.

In order to learn about substituent effects, activation parameters were determined for the isomerization of the parent 1-nitropyrazole **1a**, and for the 3-phenyl (**1d**) and 3-nitro derivative (**1f**), in nitrobenzene solution. In addition, the effect of variation in *position* of a (methyl) substituent was examined by measuring the activation parameters for the rearrangement of the 4- and 5-methyl derivatives **1g** and **4**, in *o*-nitrotoluene solution. Again, in all cases first-order behavior was observed.

The kinetic data for the rearrangement of **4** were corrected

Table I. Rate Constants and Activation Parameters for the Rearrangement of 3-Methyl-1-nitropyrazole (1b) in Various Solvents

Solvent	$10^4 k$, s^{-1} (140 °C)	$\Delta H^{\ddagger}$,[a] kcal mol^{-1}	$\Delta S^{\ddagger}$,[a] eu
n-Decane	3.4[b]	29.7	−3
Mesitylene	3.8		
Anisole	3.6		
Nitrobenzene	3.5	33.9	+7
N-Methylformamide	4.6		
Propylene glycol	6.4	30.5	0

[a] Temperature range 130–170 °C; parameters calculated for 150 °C. [b] The same rate constant was found in 0.08 and 0.008 M solutions.

Table II. Rate Constants and Activation Parameters for the Rearrangement of Some Substituted *N*-Nitropyrazoles in Nitrobenzene

Compd	Substitution	Temp, °C	$10^4 k_{150°}$, s^{-1}	$\Delta H^{\ddagger}$,[a] kcal mol^{-1}	$\Delta S^{\ddagger}$,[a] eu
1a		150–190	0.7	34.9	+4
1b	3-Methyl	130–170	9.3	33.9	+7
1d	3-Phenyl	110–140	72[c]	30.2	+2
1f	3-Nitro	160–200	0.3[c–e]	37[d,e]	+6[d,e]
1g	4-Methyl	150–190[b]	0.7[e]	35.8[e]	+6[e]
4	5-Methyl	130–160[b]	11[f]	32.7[f]	+4[f]

[a] Calculated for 150 °C. [b] In *o*-nitrotoluene rather than nitrobenzene. [c] Extrapolated from Arrhenius parameters. [d] Approximation (owing to poorly reproducible GLC analyses). [e] Not corrected for concurrent denitration (see text); denitration of **1g** ~10% at 150 °C, ~20% at 190°. [f] Corrected for concurrent $N_1 \rightarrow N_2$ nitro migration.

for the concurrent (slow) $N_1 \rightarrow N_2$ ($\rightarrow C_3$) nitro shift (see Experimental Section). For this side reaction approximate activation parameters could be calculated: log $A \approx 16$ and $E_A \approx 40$ kcal mol^{-1}. Kinetic data for the other rearrangements are based merely on decay of starting material. Hence, denitration, as observed on thermolyzing **1f** and **1g**,[3] is not treated as an independent side reaction (vide infra).

Results are summarized in Table II.

Although in solvents of entirely different character $k_{140°}$ only varies within a twofold range (Table I); the solvent effect on the activation parameters is evident. As the starting materials have distinct dipole moments (~4.0 D for **1b**, benzene solution),[1a] the higher $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values in nitrobenzene than in *n*-decane can be understood if the transition state for the rate-determining step has less (di)polar character than the starting material. In nitrobenzene, solvation lowers the energy content of the initial state relative to that in *n*-decane, while for the transition state the differences in solvation are small(er). The relatively high activation entropy in nitrobenzene solution also is a result of decreased solvation in the transition state. The rather low activation parameters observed for the rearrangement of **1b** in propylene glycol may result from hydrogen bonding interactions in the probably 3*H*-pyrazole-like transition state.

In the light of the above considerations, a transition state with a marked degree of charge separation is highly unlikely. This also follows from the small substituent effects found (Table II): the fact that a 3-phenyl substituent affects the activation energy more than 3-nitro is incompatible with a polar transition state.

Thus, the most obvious possibilities are those of a concerted NO_2 migration, or migration via an intimate radical pair. A concerted reaction involving a cyclic transition state normally has $\Delta S^{\ddagger} < 0$, although for, e.g., [1,5] sigmatropic shifts in *cyclo*pentadienes, values up to +6 eu have been reported.[18] As suggested by both dipole moments and ultraviolet spectra,[1a] the N–NO_2 bond in *N*-nitropyrazoles has a restricted rotational freedom. Hence, the entropy content of the transition state need not be less than that of the initial state. As the activation parameters in *n*-decane are the least affected by solvation, they are the most appropriate to consider. The value of −3 eu found for the rearrangement of **1b** in *n*-decane tallies, in our opinion, with a sigmatropic NO_2 migration.

The magnitude of the activation energy is also more compatible with a concerted rearrangement than with a radical-pair process. The value of the N–NO_2 bond dissociation energy is unknown, but *N*-nitropyrazoles may be compared with dialkylnitroamines. For $D_{(N-NO_2)}$ in *N*,*N*-dimethylnitroamine, values ranging from 41 to 53 kcal mol^{-1} have been reported.[19] On the basis of the heats of formation of dimethylnitroamine ($\Delta H^{\circ}_{f(g)} = 0$)[20] and the dimethylamino[21] and nitrogen dioxide[22] radicals ($\Delta H^{\circ}_{f} = +39$ and +8, respectively), we expect $D_{(N-NO_2)} \approx 47$ kcal mol^{-1}. Consequently, for *N*-nitropyrazoles a N–NO_2 bond strength of 45–50 kcal mol^{-1} seems realistic. The $\Delta H^{\ddagger}$ values for the N → C NO_2 migrations do not exceed 37 kcal; moreover, $\Delta H^{\ddagger}$ for the rearrangement of **1b** in *n*-decane is only 30 kcal mol^{-1}. The difference of ≥15 kcal with the (estimated) bond dissociation energy is thought to be sufficient for excluding N–NO_2 bond homolysis as the rate-determining step.

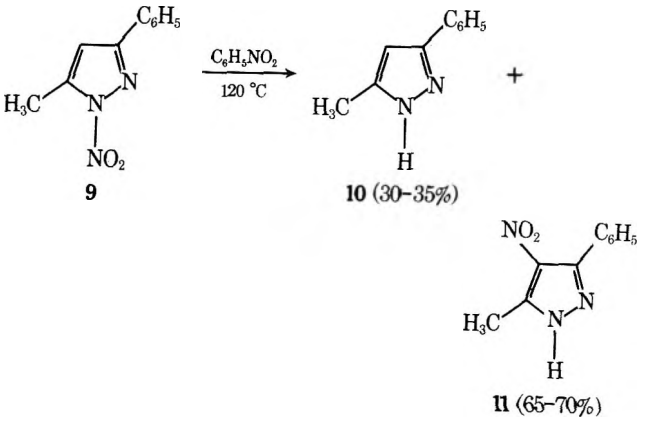
To reveal possible "borderline" character of the mechanism, thermolyses of the methyl substituted *N*-nitropyrazoles **1b**, **1g**, and **4** were performed in benzene solution, and the reaction mixtures were analyzed for *N*-phenylpyrazoles, diagnostic for free pyrazolyl radicals.[9] *N*-Phenylpyrazoles were found to be present at extremely low levels (≪0.1%) only (see Experimental Section). Perhaps impurities have played a part. However, if the proportions of *N*-phenylpyrazoles are considered to be correct indications for competitive N–NO_2 bond homolysis, and accepting log $A = 16$, the corresponding rates lead to $E_A \approx 45$ kcal mol^{-1}, in reasonable agreement with the estimated bond strength. Hence, homolytic scission of the N–NO_2 bond can be considered as an unimportant parallel reaction of the (apparently molecular) N → C NO_2 migration.

Recapitulating, the best fitting mechanism for the thermal *N*-nitropyrazole rearrangement involves a rate-determining, concerted migration of NO_2 giving a nonaromatic 3-nitro-3*H*-pyrazole (**3**) as intermediate (cf. Scheme II). This endothermal step is followed by rapid tautomerization to give a 3(5)-nitropyrazole **2**; hence the driving force for the overall isomerization is the greater stability of a *C*-nitro- as compared to a *N*-nitropyrazole.[23]

In the first step of the rearrangement, the nitro group has to move out of the pyrazole plane; therefore, the nitro migration may be classified as a symmetry-allowed suprafacial [1,5] sigmatropic shift[24] (cf. [1,5] migrations in cyclopentadienes). The $N_1 \rightarrow N_2$ nitro migration as observed during the isomerization of **4** might well be a *suprafacial* (i.e., over the pyrazole plane) shift too, rather than an in-plane migration. Although a planar process is the least motion mode and aromaticity of the pyrazole ring is conserved, it is unlikely as it, when concerted, is a $[{}_{\sigma}2_s + {}_{\omega}2_s]$, symmetry forbidden process.[24,25] The relatively high activation energy for a $N_1 \rightarrow N_2$ nitro shift may be a result of the interaction of *three* nitrogen centers in the transition state.

Although the N → C nitro migration apparently is a concerted process, the rather small (and insufficiently examined as yet) *substituent* effects (see Table II) might be indicative for polar contributions to the pericyclic transition state. So rate enhancement by a 3-methyl and retardation by a 3-nitro substituent is suggestive of a *minor* contribution of bicyclic

Scheme VI



structure A (vide supra). On the other hand, the effect of the position of a (methyl) substituent is not easily understood.

As mentioned above, isomerization of *N*-nitropyrazoles is sometimes accompanied by denitration. Especially this is the case when the 4 position is substituted (cf. ref 3). It is difficult to imagine how a substituent at the 4 position should affect the first step of the isomerization. During the second step (that of rearomatization), however, the nitro group has to return in the pyrazole plane. From dissociation constants and ultraviolet spectra of "ortho"-substituted *C*-nitropyrazoles[26] it follows that these compounds are strained.[27] Hence the activation barrier for tautomerization into 4-substituted 3(5)-nitropyrazoles may well be increased, and alternative reactions may take place. To test this thesis, the thermolysis of 5-methyl-1-nitro-3-phenylpyrazole (**9**) was studied. Neither 5-methyl-1-nitropyrazole (**4**) nor 1-nitro-3-phenylpyrazole (**1d**) give denitration, but the expected rearrangement product of **9**, 3(5)-methyl-4-nitro-5(3)-phenylpyrazole (**11**), is highly strained, and denitration should be observed. Heating **9** in nitrobenzene at 120 °C indeed yields **11**, but also for ~30% the denitrated pyrazole **10** (see Scheme VI); $k_{120°}$ for the disappearance of **9** is $\sim 4.2 \times 10^{-4}$ s^{-1} (see Experimental Section), and the product ratio **10**:**11** does not depend on the degree of conversion (tallying with the observation that **11** is stable under the experimental conditions). Hence, it is likely that the denitration reaction competes with the rearomatization step(s). The way in which the nitro group is lost is, as yet, far from clear, however. Possibly some radical pathway obtains.[28]

The denitration accompanying isomerization of 1,3-dinitropyrazole (**1f**) may not be due to steric factors. As addition of quinoline appeared to suppress this side reaction,[30] a heterolytic mechanism is indicated. Here, the product, **2f**, with $pK_a = 3.1$,[26] may be acidic enough to entail protodenitration.[31]

In conclusion, the mechanism suggested earlier for the thermal *N*-nitropyrazole rearrangement seems in accord with all experimental data: the rearrangement is intramolecular; solvent and substituent effects rule out a polar (or ionic) transition state for the rate-determining NO_2 migration step, while the low $\Delta H^{\ddagger}$ values make a radical-pair process highly unlikely. The most plausible mechanism, then, is that of sigmatropic NO_2 migration.

Experimental Section[32]

Materials. The syntheses of the *N*-nitropyrazoles used for the kinetic measurements, as well as those for the *C*-nitropyrazoles used as reference materials, have been described in ref 2 and 3. Other pyrazoles, such as 3(5)-methyl-5(3)-phenylpyrazole (**10**), were synthesized by standard procedures. The solvents used for the kinetic measurements were redistilled over either a spinning band column or a 1-m Vigreux column, *n*-decane after treatment with concentrated sulfuric acid. Other chemicals (including those used as internal standard), being high-grade commercial products, were used as such.

3(5)-Deuterio-5(3)-methylpyrazole.[29] A solution of 5 g of 3(5)-methylpyrazole in 25 ml of 1 N sodium deuteroxide (prepared by dissolving sodium in deuterium oxide, 99.75%) was heated in an autoclave at 150 °C for 4 h. The reaction mixture was neutralized with deuterated (98–99%) trifluoroacetic acid, and the deuterated pyrazole was isolated by means of continuous extraction (15 h) with methylene chloride, followed by evaporation of the solvent; this alkaline exchange was repeated once. The deuterated pyrazole was then refluxed for 15 h in 1 N aqueous sulfuric acid, and worked up (after neutralization with sodium bicarbonate) by continuous extraction with methylene chloride. This acid exchange was repeated once. The resulting pyrazole was distilled in vacuo: yield 3.2 g; bp 105 °C (18 mm); NMR (60 MHz, $CDCl_3$ solution) δ 5.8 (s, 1, 4-H) and 2.1 ppm (s, 3, CH_3); isotopic composition (MS analysis,) 7.4% d_0, 86% d_1, and 6.6% d_2.

5-Deuterio-3-methyl-1-nitropyrazole (8).[29] A preformed mixture of 6 ml of acetic anhydride and 2.5 ml of nitric acid (100%) was added carefully to a solution of 2.0 g of 3(5)-deuterio-5(3)-methylpyrazole in 2 ml of acetic acid at 0 °C. After 2 h, the reaction mixture was poured onto ice and neutralized with potassium carbonate, and the resulting precipitate was collected through filtration. The crude product (1.4 g) was crystallized from hexane: mp 54–55 °C; NMR (100 MHz, $CDCl_3$) δ 6.2 (s, 1, 4-H) and 2.3 ppm (s, 3, CH_3); *no* 5-H signal could be detected. Accurate MS analysis appeared to be impeded by D/H randomization in the mass spectrometer.

Measurement of the Kinetic Isotope Effect.[29] About equal quantities of both the deuterated **8** and the nondeuterated 3-methyl-1-nitropyrazole (**1b**) were dissolved in hexachloroacetone; *p*-dichlorobenzene was added as internal standard. NMR spectra (100 MHz) were recorded before and after heating of the solution in an oil bath at 140 °C. The results of a typical experiment are as follows.[33]

	Integrated signals (relative to internal standard)			Obsd ratio[b]
	5-H	4-H	4′-H[a]	**1b**/**8**
Initial solution[c]	0.761	1.412	—	1.17
After 20 min at 140°C	0.514	0.951	0.439	1.18

[a] 4-Proton from the rearrangement product. [b] Calculated from 5-H/(4-H − 5-H). [c] Weight ratio **1b**/**8** = 1.05.

Kinetic Measurements. A. Determination of the Rate Constants. General Procedure. A small, thin-wall tube, containing ~0.5 ml of a ca. 0.1 M solution of the *N*-nitropyrazole and an internal standard[34] in the appropriate solvent, was placed in a thermostated oil bath; a small stream of nitrogen was passed over. Aliquots were removed at regular time intervals and analyzed by GLC (using a 2 m × 0.125 in., OV-17 on Gas-Chrom Q column,[35] at temperatures at which rearrangement of the *N*-nitropyrazole was negligible, normally 120–150 °C). The isomerizations were followed for about 2 half-lives. The relative amounts of *N*-nitropyrazoles present in the samples (C_t) were calculated from the peak areas. First-order rate constants were calculated from plots of ln C_0/C_t vs. time.

B. Correction of the Kinetic Data for the Rearrangement of 5-Methyl-1-nitropyrazole (4). To correct for the concurrent (slow) $N_1 \rightarrow N_2$ ($\rightarrow C_3$) nitro shift, the product ratios 3(5)-methyl-5(3)-nitropyrazole (**2b**)/3(5)-methyl-4-nitropyrazole (**5**), representing $k(N_1 \rightarrow N_2)/k(N_1 \rightarrow C_5)$, were determined by analyzing the reaction mixtures after more than 10 half-lives by GLC, using standard mixtures of the isomeric *C*-nitropyrazoles. Although the *C*-nitropyrazoles were incompletely separated, $k(N_1 \rightarrow C_5)$ could be calculated with appropriate accuracy. From the (less accurate) values of $k(N_1 \rightarrow N_2)$, activation parameters for this isomerization were calculated (vide supra).

Thermolysis of *N*-Nitropyrazoles in Benzene Solution. Solutions (ca. 5%) of the relevant *N*-nitropyrazoles in benzene, containing 0.01% of *p*-di-*tert*-butylbenzene as internal standard, were heated in sealed tubes. The resulting solutions were analyzed by GLC on a 55-m capillary OV-17 column. Quantitative analyses were made for *N*-phenylpyrazoles only: 3-methyl-1-nitropyrazole (**1b**), 2 h at 150 °C, gave ca. 0.006% of 3-methyl-1-phenylpyrazole (**6**) (close to the lower limit of detection; the 5-methyl isomer **7** could not be detected); 5-methyl-1-nitropyrazole (**4**) gave, under the same conditions, ca. 0.015% of a mixture of the isomeric *N*-phenylpyrazoles **6** and **7**; 4-methyl-1-nitropyrazole (**1g**), 2 h at 190 °C, gave ca. 0.03% of 4-methyl-1-phenylpyrazole; in the latter reaction mixture, semiquantitative analysis revealed ~16% of 4-methylpyrazole, 0.7% of nitrobenzene, and ~0.1% of biphenyl.

5-Methyl-1-nitro-3-phenylpyrazole (9)[29] was prepared from **10** (2 g) by nitration in acetic acid (12 ml) with acetyl nitrate (1.7 ml of HNO_3, *d* 1.52, and 4 ml of acetic anhydride), during 2 h at room temperature. After working up with ice-cold water, filtration, and recrystallization from methanol, 0.9 g of **9** was obtained: mp 99–100 °C; ir (KBr) 1615 and 1265 cm^{-1} (NNO_2); NMR ($CDCl_3$) δ 7.6 (m, 5, C_6H_5), 6.56 (s, 1, 4-H), and 2.68 (s, 3, CH_3].

Anal. Calcd for $C_{10}H_9N_3O_2$: C, 59.10; H, 4.46; N, 20.68. Found: C, 59.02; H, 4.67; N, 20.48.

Thermolysis of 9.[29] **A. Preparative Scale.** A solution of 0.8 g of **9** in 10 ml of chlorobenzene was heated for 4 h at 110 °C under a nitrogen atmosphere. After evaporation of the solvent, the products were chromatographed over a silica gel column using achloroform–ethyl acetate mixture as eluent. In addition to 0.18 g of unreacted **9**, 0.35 g of 3(5)-methyl-4-nitro-5(3)-phenylpyrazole (**11**) and 0.20 g of denitrated product **10** were isolated. Compound **11** was recrystallized from benzene and had mp 140 °C; ir (KBr) 1600 and 1360 cm^{-1} (CNO_2); NMR ($CDCl_3$) δ 8.27 (s, 1, N–H), 7.36 (s, 5, C_6H_5), and 2.26 (s, 3, CH_3).

Anal. Calcd for $C_{10}H_9N_3O_2$: C, 59.10; H, 4.46; N, 20.68. Found: C, 59.42; H, 4.77; N, 20.14.

B. NMR Scale. A 0.2 M solution of **9** in nitrobenzene, containing *p*-di-*tert*-butylbenzene as internal standard, was heated (under a nitrogen atmosphere) in a thermostated oil bath at 120 °C. Samples were withdrawn at six 15-min intervals. Product compositions were determined via careful integration of NMR (100 MHz) spectra.

Registry No.—**1a,** 7119-95-1; **1b,** 31163-84-5; **1d,** 38859-26-6; **1f,** 38858-81-0; **1g,** 38858-82-1; **4,** 31163-85-6; **8,** 58311-77-6; **9,** 58311-78-7; **10,** 3440-06-0; **11,** 58311-79-8; 3(5)-deuterio-5(3)-methylpyrazole, 58311-80-1; 3(5)-methylpyrazole, 1453-58-3.

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(27) Although strained, the investigated "ortho"-substituted *C*-nitropyrazoles were stable under the experimental conditions for the rearrangement reactions.

(28) In the product of thermolysis of **1g** in anisole (2 h at 190 °C), 0.7% of nitroanisole (mainly *m*- and *p*-; GLC analysis[29]) was found to be present. Cf. thermolysis of **1g** in benzene, yielding 0.7% of nitrobenzene (see Experimental Section). Note also that in the latter case only a trace amount of 4-methyl-1-phenylpyrazole is formed; this seems to exclude formation of NO_2 via homolysis of starting compound **1g**.

(29) This experiment was performed by M. Timmer, this laboratory.

(30) In contrast, addition of quinoline to 4-methyl-1-nitropyrazole (**1g**) seems to have no effect on the denitration reaction (GLC analysis).[29]

(31) When thermolyzing **1f** in benzene at 190 °C, ca. 1% of nitrobenzene is formed; the use of anisole as a solvent (170 °C) led to 2–3% of *o*- and *p*-nitroanisole (ratio ca. 1.5:1, GLC analysis),[29] indicative of electrophilic nitration. Compare J. G. Hoggett, R. B. Moodie, J. R. Penton, and K. Schofield, "Nitration and Aromatic Reactivity", Cambridge University Press, New York, N.Y., 1971, p 95.

(32) The following instruments were used: Varian Aerograph 1400 and Hewlett-Packard HP 5700 gas chromatographs; JEOL PS-100 and Minimar NMR apparatus; an AEI-MS 902 mass spectrometer; and a Beckman IR-10 spectrophotometer.

(33) From these data it can also be concluded that (1) the rate of the rearrangement in hexachloroacetone is about 3×10^{-4} s^{-1}, comparable to that in the other solvents used (cf. Table I), and (2) the rearrangement in hexachloroacetone proceeds cleanly ($4\text{-}H_{t=0} = 4\text{-}H_{t=20} + 4'\text{-}H_{t=20}$).

(34) The following internal standards were used: nitrobenzene (rearrangement of **1b** in *N*-methylformamide and propylene glycol); *n*-tridecane (**1b** in *n*-decane); methyl myristate (rearrangement of **1d**); and *n*-pentadecane (all other cases).

(35) To follow the rearrangement of **1d**, a comparable 0.5-m column was used.

Acylanthranils. 1. The Pathway of Quinazolone Formation in the Reaction of Acylanthranils with Anilines[1]

L. A. Errede

Central Research Laboratories, 3M Company, St. Paul, Minnesota 55101

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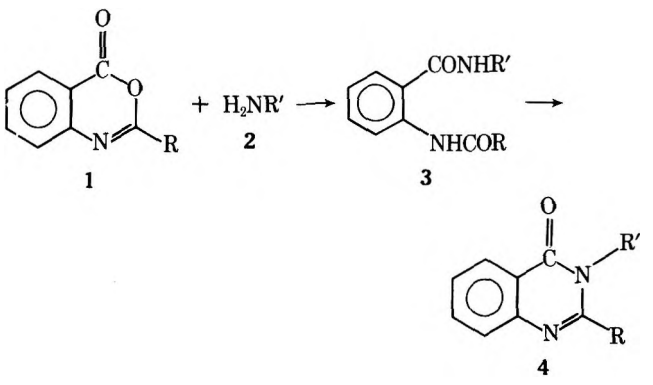
Reinvestigation of the reaction of benzoxazinones, **1** (i.e., acylanthranils), with anilines, **2**, to give *o*-acylamidobenzanilides, **3**, and/or quinazolones, **4**, has shown that the accepted pathway for the sequential formation of **4** from **3** is not correct. These products are formed concurrently via alternative pathways. The precursor of **4** is not **3**, but rather a *N*-(2-carboxyphenyl)-*N'*-arylacylamidine, **5**, a heretofore unobserved intermediate which is converted to **4** even at room temperature.

Interest in the reaction of benzoxazinones, **1**, with primary amines, **2**, has been renewed owing to the potential use of the products produced thereby as physiologically active compounds[2] or as thermostable polymers.[3,4] The early work with this reaction was done ca. 1900 by Heller, Bogert, and others,[5] who reported that *o*-acylamidobenzamides, **3**, and/or the corresponding quinazolones, **4**, were the major products. They proposed that **4** was formed from **3** during the course of this reaction, which usually was carried out at reflux temperature in a solvent such as toluene. This sequential pathway appeared to be consistent with all the observed results, and is still recorded in modern reference books[6] as the accepted pathway as shown below:



A considerable amount of the early work was done using 2-methyl-4*H*-benzoxazin-4-one (**1a**). This compound was given the trivial name acetylanthranil,[5] presumably to emphasize that it is the anhydride obtained conveniently from acetylanthranilic acid by cyclodehydration in acetic anhydride at reflux temperature. Acetylanthranil is an interesting semiacid anhydride that undergoes many of the reactions of true acid anhydrides, but at a slower rate.

Initially,[4] our own research was directed toward high-performance polymers from bifunctional acylanthranils and diamines. In the course of this research, it was of interest to establish how easily the neutral diamide form, **3**, could be converted thermally to the basic quinazolone form, **4**, as per the proposed pathway. A set of acylamidobenzamides were used as model compounds for these conversions, which were monitored by differential thermal analysis (DTA). The data are shown in Table I. In view of the accepted pathway, it was surprising to note that the minimum temperature required for thermal cyclodehydration to the corresponding quinazolone was about 250 °C. Since this minimum temperature is more than 100 °C above the highest temperature used to react acylanthranils with amines, the accepted pathway, which requires that **4** be produced sequentially from **3** under relatively mild conditions, became suspect, and this uncertainty required clarification.

We observed that acetylanthranil (**1a**) reacts with amines at an appreciable rate even at room temperature, so that the reflux temperatures employed by the earlier researchers were unnecessary, and may even have obfuscated proper interpretation of their results. In the reaction of **1a** with aniline, it was noticed that some of the product separated from solution as a white precipitate easily isolated by filtration. The dry powder melted sharply at 115–116 °C with evolution of a gas, and its elementary analysis was consistent with the empirical formula $C_{15}H_{14}O_2N_2$, which corresponds to a one-to-one adduct, **5a**, of acetylanthranil and aniline. This adduct dissolved in warm acetone–water solution, but it decomposed slowly in this solvent to give equivalent amounts of *N*-acetylanthranilic acid, **6**, and aniline. It dissolved in warm dilute aqueous $NaHCO_3$ with evolution of some CO_2. It dissolved even more rapidly in cold dilute NaOH and in cold dilute HCl, indicating that the compound was some form of internal salt or zwitterion. The salt is unstable in aqueous solution, especially at pH >7, and a precipitate begins to form within 0.5 h and appears to be complete within 4 h. This precipitate, which represented 80% of the dissolved salt, was identified as *N*-phenyl-2-methylquinazol-4-one (**4a**). The rest was isolated as *N*-acetylanthranilic acid and aniline in about equivalent amounts. A sample of the salt product was converted by fusion at ca. 130 °C to give almost quantitatively **4a** with evolution of an equivalent amount of water.

The ir spectrum of the adduct, **5a**, in KBr confirms a saltlike structure (broad band at 3–4 and at ca. 6.3 μ). It rules out the presence of amide carbonyl groups (no absorption band at 5.7–6.0 μ), but supports the presence of NH (band at 2.9 μ), –C=N– (band at 6.1 μ), monosubstituted phenyl (band at 14.4 μ), and an ortho-disubstituted phenyl group (12.9 μ). The NMR spectrum of the adduct dissolved in alkaline D_2O indicates only one form of CH_3 group (τ 8.12), and a complex aromatic pattern in the region τ 1.6–3.2. It was concluded, therefore, that the adduct, **5a**, of acetylanthranil and aniline is an internal amidine salt.

Only about half the acetylanthranil was recovered as insoluble **5a**. The rest remained in the excess aniline used as solvent. In order to recover the other half, the mother liquor was concentrated almost to dryness by distillation at 80 °C in an evacuated system. The residue was a mixture whose major component (about 60%) was **4a**. The other major component (about 30%) was identified as *N,N'*-diphenylacetamidine (**7**), which was produced apparently by aniline exchange with the 2-carboxyaniline group as indicated in Chart I.

When **5a** was subjected to reaction conditions approximating those used by the early investigators, namely in solvents such as pyridine or toluene and some amine as catalyst at reflux temperatures, it was converted within mimutes to **4a**. This result is in sharp contrast to the observation made earlier that ortho diamides of type **3** are stable under these conditions and indeed are not converted to **4** unless consid-

Table I. Thermal Conversion of o-(Acylamido)benzamides (3) to Quinazolones (4)

R′	R	3 mp, °C	4 mp, °C	Temp of convn, °C, by DTA[a]	Registry no. 3	Registry no. 4
Ph	CH_3	160–162	147–148	300–310	54364-31-7	2835-23-1
Ph(CO_2H)-*o*	CH_3	215–216	255–257	340–360	58426-37-2	4005-06-5
Ph	Ph	280–281	120–121	290–310	18543-23-2	22686-82-4
H	CH_3	187–188	240–241	250–270	16353-13-2	1769-24-0
$(CH_2)_6NHCOPh$-($NHCOCH_3$)-*o*	CH_3	203–204	174–177	340–370	58426-47-4	58426-48-5

[a] Differential thermal analysis.

Chart I

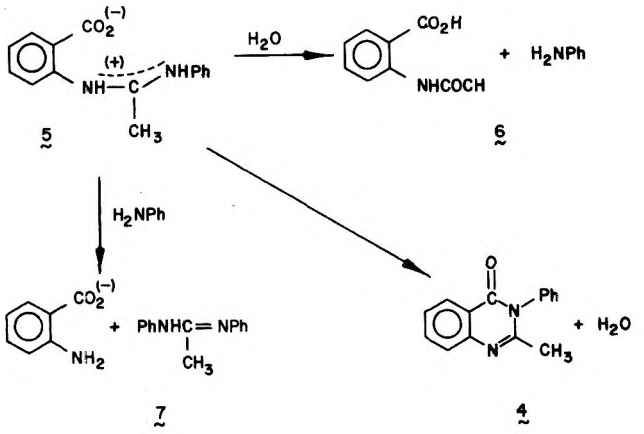
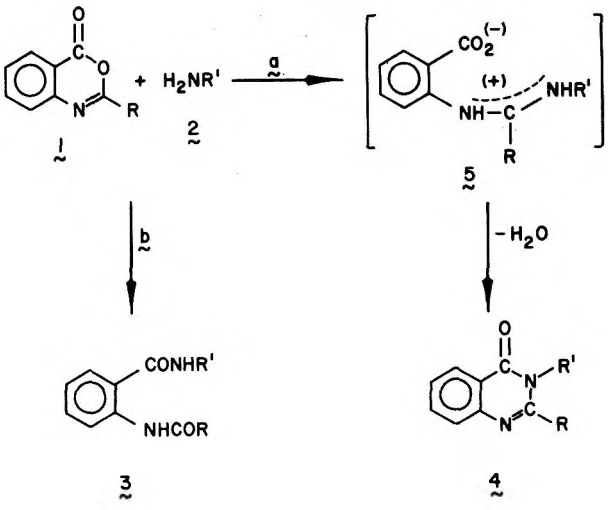


Chart II



erably more strenuous conditions are employed, such as fusion above 250 °C.

When **1a** was allowed to react at room temperature with *p*-toluidine (**2b**) and with *p*-(*N*,*N*-dimethylamino)aniline (**2c**) in a neutral solvent, the corresponding amidine salts (**5b** and **5c**) were isolated in very good yields (>90%). In these cases, the salt product was separated by filtration and the mother liquor was then diluted with ether to cause precipitation of the soluble portion, thereby precluding conversion to the corresponding quinazolone, **4**, or diarylacetamidine, **7**, which occurs at higher temperatures and in excess amine.

When benzoylanthranil (i.e., 2-phenyl-4*H*-3,1-benzoxazin-4-one, **1b**) was made to react with aniline in benzene at reflux temperature, *o*-acetamidobenzanilide (**2b**) was obtained almost exclusively, which is in sharp contrast to the results obtained with acetylanthranil (**1a**). The reactivity of **1b** is considerably less than that of **1a**, and consequently, the higher temperature was required to effect conversion to products within a reasonable time interval. This temperature difference, however, as well as the change from a methyl substituent to a phenyl at the 2 position of the anthranil, may account for the sharp change in selectivity, and further investigation is required to establish the cause of the inversion in selectivity. Nevertheless, the results do show that the products **3** and **4** are formed via alternate pathways a and b, as shown in Chart II, and not sequentially as believed earlier.

Although results reported here for **1a** and **1b** represent extreme cases in selectivity, they are not necessarily typical. The results obtained by others,[2,5,6] who caused numerous acylanthranils to react with numerous amines, indicate that a mixture is usually produced, with **3** as the major component instead of **4**. These results infer that b is the preferred pathway which is consistent with the known relative reactivity of >C=O vs >C=N– groups. More work is planned, however, to understand better the parameters that affect selectivity and overall rate of reaction.

Although the amidine salts of type **5** have never previously been isolated, one was postulated by Scherrer and Beatty[7] as a very short-lived intermediate in the reaction of 2,3-diphenyl-4(3*H*)-quinazolinone (i.e., *N*,2-diphenylquinazol-4-one) in alcoholic NaOH to give aniline and anthranilic acid. In a sense, the Scherrer reaction is the reverse of that discussed in this paper.

Experimental Section

A. Preparation of Acetylanthranil (1a). A solution of anthranilic acid (1 mol) in acetic anhydride (0.5 l.) was made to react at reflux temperature for 2 h. The excess solvent was removed by distillation at atmospheric pressure. The residue was separated by distillation under vacuum and the fraction boiling in the range 125–132 °C at 8 mmHg pressure was collected as an oil that solidified to a white solid. The solid was recrystallized from heptane to give acetylanthranil in the form of long, white, dense needles (mp 81–82 °C, lit. mp 81–82 °C[8]) in 85% yield.

B. Reaction of Acetylanthranil (1a) with Anilines. 1. With Aniline (2a) to Give 5a, 4a, and 7. Acetylanthranil (26 g) (**1a**) was dissolved at room temperature in aniline (100 g) (**2a**) to give a clear solution, which soon became turbid as a white precipitate began to form throughout the solution. Precipitation appeared to be complete within 4 h, and the mixture was separated by filtration. The precipitate was slurried in ether and recollected by filtration to yield 22 g of product as a white powder (mp 115–116 °C).

Anal. Calcd for $C_{15}H_{14}O_2N_2$: C, 70.85; H, 5.55; N, 11.01; O, 12.60. Found: C, 70.7; H, 5.9; N, 10.9; O, 12.5.

The ir and the NMR spectra are consistent with the amidine salt structure **5a** as discussed in the body of this report.

A sample of **5a** (2 g) was dissolved at room temperature in a minimum amount of 2% aqueous NaOH and then diluted twofold. The clear solution became cloudy within 0.5 h and precipitation appeared to be complete within 8 h. The product was collected by filtration and recrystallized from heptane to give *N*-phenyl-2-methylquinazol-4-one (**4a**) in the form of pearl-white platelets (1.7 g, mp 147–148 °C). The compound was identified by its ir spectrum and elemental analysis.

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86; mol wt. 236.38. Found: C, 76.6; H, 5.6; N, 11.8; mol wt, 242.

The compound was converted to its hydrochloride salt by reaction with HCl in ether. The salt was recrystallized from hot water to give the hydrochloride of **4a** in the form of pearl-white platelets (mp 275–277 °C).

Anal. Calcd for $C_{15}H_{13}N_2OCl$: Cl, 13.5. Found: Cl, 13.5.

Another sample of **5a** (1 g) was fused at 120 °C for about 0.5 h during which time an equivalent amount of water was liberated, and the melt resolidified as a white solid. The solid was recrystallized to give **4a** in the form of white flakes (0.9 g, mp 147–148 °C).

The aniline solution, from which **5a** was removed by filtration, was evaporated to dryness at <1 mmHg pressure and 80 °C. The residue was digested with 10% aqueous HCl, leaving a white, saltlike residue (15 g) which was recrystallized from hot water to give the hydrochloride of **4a** in the form of pearl-white platelets (mp 275–277 °C; no depression with an authentic sample). The aqueous acid extract was neutralized with NaOH. A yellowish-white powder precipitated and was removed by filtration. This powder (2.5 g) was recrystallized from heptane to give *N,N'*-diphenylacetamidine (**7**) in the form of white crystals (mp 126–127 °C; no depression with an authentic sample).[9] The compound was also identified by its ir spectrum, identical with that of an authentic sample.

When 0.16 mol of **1a** was made to react with **2a** as solvent, 54% of **1a** was isolated as **5a**, 30% as **4a**, and 15% as **7**.

2. In *p*-Toluidine (2b) to Give 5b. Acetylanthranil (0.1 mol) was dissolved in **2b** (0.6 mol) to give a clear solution which became turbid soon thereafter as the product began to precipitate from solution. Precipitation appeared to be complete after 4 h. The precipitate (mp 119–120 °C) was collected by filtration and washed with Et_2O. The mother liquor containing the excess aniline was diluted 20-fold with ether and additional precipitate (mp 119–120 °C) formed which was also collected by filtration. The combined precipitates represented a 95% yield of *N*-(2-carboxyphenyl)-*N'*-(*p*-tolyl)acetamidine (**5b**), identified by its ir spectrum and its elemental analysis.

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 72.0; H, 6.1; N, 10.3.

A sample of **5b** (1.0 g) was dissolved in 0.5% aqueous base to give a clear solution. A few minutes thereafter, the solution became cloudy with the formation of the quinazolone, which precipitated as a white powder. Precipitation appeared to be complete within 1 h, and the product (0.9 g) was collected by filtration, dried, and recrystallized from heptane to give *N*-(*p*-tolyl)-2-methylquinazol-4-one (**4b**) in the form of long, flat needles (mp 151–152 °C). The assigned structure of **4b** was verified by its ir spectrum.

3. In *p*-(Dimethylamino)aniline (2c) to Give 5c. Acetylanthranil (0.1 mol) was dissolved at room temperature in **2c** (0.2 mol) to give a clear solution, which became a semisolid mixture within 4 h. The mixture was diluted with Et_2O and separated by filtration. The amount isolated represented 96% of the expected amidine salt, **5c**, whose assigned structure was verified by its ir spectrum and its elemental analysis.

Anal. Calcd for $C_{17}H_{19}O_2N_3$: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.5; H, 6.6; N, 14.2.

The salt began to melt at 160 °C, but it was converted at this temperature to the corresponding quinazolone, **4c**, which solidified from the melt. A sample of the amidine salt (1 g), contained in a test tube, was fused in an oil bath kept at 180 °C. The salt melted rapidly with evolution of water vapor which was condensed on the cool upper portion of the test tube. The melt resolidified within a few minutes. The product was recrystallized from ethanol–water solution to give *N*-(*p*-dimethylaminophenyl)-2-methylquinazol-4-one (**4c**), in the form of white crystals (0.8 g, mp 227–228 °C). The compound was identified by its ir spectrum and elemental analysis.

Anal. Calcd for $C_{17}H_{17}ON_3$: C, 73.09; H, 6.14; N, 15.04; mol wt, 279.4. Found: C, 73.1; H, 6.3; N, 14.9; mol wt, 278.

Another sample of **5c** (2.0 g) was dissolved in dilute aqueous NaOH. Precipitation of the quinazolone, **4c**, began within 5 min and was complete within 1 h. The product (1.8 g) was identified as **4c** by its ir spectrum and its melting point, 227–228 °C, which showed no depression when mixed with the product obtained by fusion.

Reaction of Benzoylanthranil (1b) with Aniline to Give *o*-Benzamidobenzanilide (3b). Benzoylanthranyl (3 g, mp 122 °C), which was prepared according to the procedure of Anschutz,[10] was allowed to react overnight at reflux temperature with aniline (3 g) in benzene (50 ml). The product separated in the form of a white powder (3.8 g, mp 286–287 °C). It was identified as *o*-benzamidobenzanilide (**3b**) by its melting point and ir spectrum, which were identical with those of an authentic sample.

Acknowledgment. The author is indebted to Dr. J. J. McBrady for interpretation of the ir and NMR spectra.

Registry No.—**1a**, 525-76-8; **1b**, 1022-46-4; **2a**, 62-53-3; **2b**, 106-49-0; **2c**, 99-98-9; **4a** HCl, 52692-90-7; **4b**, 22316-59-2; **4c**, 58426-38-3; **5a**, 34264-61-4; **5b**, 58426-41-8; **5c**, 58426-42-9; **7**, 621-09-0; anthranilic acid, 118-92-3.

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Acylanthranils. 2. The Problem of Selectivity in the Reaction of Acetylanthranil with Anilines

L. A. Errede,* J. J. McBrady, and H. T. Oien

Central Research Laboratories, 3M Company, St. Paul, Minnesota 55101

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Anilines attack acetylanthranils preferentially at the carboimino center rather than at the carbonyl center despite the greater reactivity of the latter group toward nucleophilic agents. Anthranilic acid is a notable exception that gives predominantly o-(*o*-acetamidobenzamido)benzoic acid, the product produced via reaction at the carbonyl site.

Reinvestigation[1] of the reaction of benzoxazinones (i.e., acylanthranils), **1**, with anilines, **2**, showed that the diamide, **3**, and quinazolone, **4**, products are formed via alternate pathways a and b as shown in Chart II of ref 1, and not sequentially **4** from **3** as was suggested by earlier investigators.[2]

Acylanthranils undergo many of the reactions of acid anhydrides, but at a much slower rate. They can be considered in effect as cyclic mixed anhydrides that react with amines via two alternative electrophilic sites, namely at the carbonyl group to give via pathway b a neutral diamide **3**, or at the carboimino group to give via pathway a an amidine salt **5**. Presumably the reaction via both pathways is kinetically first

Table I. Reaction Products of 1 with Anilines, H_2NPhR

Aniline	R substituents	Rxn conditions: Solvent	Rxn conditions: Temp, °C	Mp, °C (yield)[f] of products: 5	4	3	a/b = 5 and/or 4/3
a	None	a	RT	115–116 (80)	147–148 (75)		>50/1
b	p-CH_3	a	RT	119–120 (85)	151–152 (73)		>50/1
c	p-$(CH_3)_2N$	a	RT	158–160 (60)	227–228 (36)		>50/1
d	p-H_2N	a	RT	96–98 (90)	226–227 (8)		>50/1
e	p-CH_3O	a	RT	123–124 (65)	267–268 (33)		>50/1
f	p-CO_2H	b	60		280–281 (30)[g]		>50/1
g	m-CF_3	c	100		139–140 (85)[g]		>50.1
h	m-OH	d	RT	130–135 (81)	122–126 (17)		>50/1
i	o-CH_3	a	RT		113–114 (85)[g]		>50/1
j	o-Et	d	RT		249–250 (55)[g]		>50/1
k	o-CH_3O	a	RT		131–132 (70)[g]		>50/1
l	2,4,6-$(CH_3)_3$	d	RT	122–123° (70)	99–100 (15)[g]		>50/1
m	2,6-$(Et)_2$	d	RT		108–109 (69)[g]		>50/1
n	o-CO_2H	e	Reflux		255–257 (5)	215–216 (92)	1/18

[a] Benzene. [b] Pyridine. [c] Neat. [d] Et_2O. [e] Toluene. [f] % acetylanthranil units isolated as product indicated given in brackets. [g] Most of the remainder of the acetylanthranil units were isolated as o-acetamidobenzoic acid indicating incomplete reaction and/or reaction with H_2O liberated via cyclodehydration of 5 to give 4.

order with respect to 1 and to 2, so that the observed product ratio should be a measure of the ratio of the rates of reaction for the corresponding pathways, i.e.

$$\frac{\text{4 and/or 5}}{3} = \frac{\text{reaction via pathway a}}{\text{reaction via pathway b}} = \frac{k_a}{k_b}$$

The results obtained by the earlier investigators,[2] who caused numerous acylanthranils to react with numerous amines, suggest that b is the preferred reaction pathway (i.e., b/a ≫ 1), which is consistent with the known relative reactivity of anhydride >C=O vs. >C=N– groups. Our own result[1] with benzoylanthranil (i.e., 2-phenyl-4*H*-benzoxazin-4-one, **1a**), was also consistent with this generality. On the other hand, the corresponding acetamidine salts were obtained exclusively when acetylanthranil (i.e., 2-methyl-4*H*-benzoxazin-4-one, **1b**) was made to react with aniline, p-toluidine, and p-dimethylaminoaniline (i.e., a/b ≫ 1), which is inconsistent with the above generality. It was of interest, therefore, to investigate this reaction further to determine which set of results was the exception and why.

To this end, it was necessary to establish a convenient separation and identification procedure, which would permit a rapid completion of the materials balance for each sample. The chemical properties of the products are sufficiently different to permit separation by conventional chemical procedures as described previously. These procedures were simplified by utilizing an equivalent amount of amine instead of an excess in a neutral solvent to ensure conversion to a product mixture of no more than three major components. The separation sequence was standardized as described in the Experimental Section. The materials balance data indicated that usually more than 95% of the reactants were recovered as one or more of three products plus o-acetamidobenzoic acid which is formed via hydrolysis of unreacted acetylanthranil. In most cases, the structural assignment of the product isolated could be verified on the basis of its ir spectrum, since the characteristic absorption patterns for each product as a class were established with model components as summarized in the Experimental Section. Experience gained in the separation of known mixtures of these components showed that small amounts of 3 might sometimes be missed, if it were present as a minor component of a mixture that was 99% 4 or its conversion product 5. Conversely, small amounts of 5 (or 4) might sometimes be missed, if it were present as a minor component of a mixture that was 98% 3. It was decided, therefore, to interpret conservatively in this and subsequent studies the isolation of 4, or its precursor 5, exclusive of 3 as a/b > 50/1, and the isolation of 3 exclusive of 4 (or 5) as a/b < 1/25. It was also decided to round all values of a/b within this range to the nearest whole number to ensure emphasis on the qualitative conclusions rather than the quantitative. The data obained in this investigation, using aromatic amines **a–n**, are summarized in Table I.

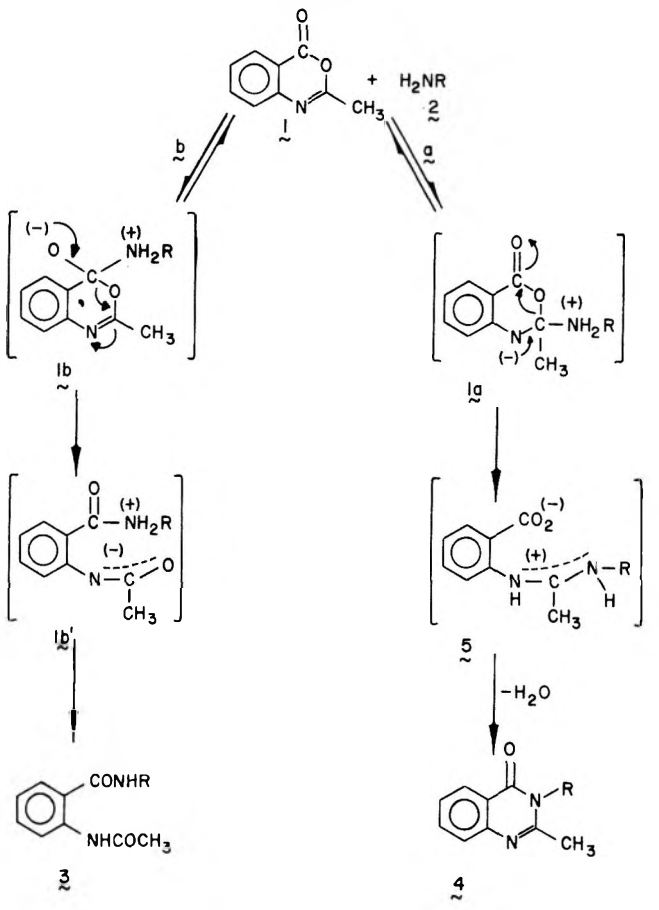
These results show clearly that anilines, with the notable exception of anthranilic acid (**2n**), attack acetylanthranil at the carboimino center rather than the carbonyl center. This generalization is contrary to that expected on the basis of the relative reactivity of the anhydride >C=O and >C=N– groups at the 4 and 2 positions of **1**, respectively. It was suggested by Katritzky[3] that the explanation may lie in the relative stability of the ionic intermediates for the alternative pathways, rather than in the competitive rates for initial attack by the nucleophile on the alternative electrophilic centers as shown for example in Chart I.

Addition of the amine to acetylanthranil gives reversibly either zwitterion intermediate **1a** or **1b**. These cyclic intermediates can open to give respectively **5**, which is relatively stable, and **1b′**, which forms **3** immediately via a proton shift. It was pointed out by one of the referees that the principal net effects in these competitive ring openings is the transfer of a negative charge from N to O, when going from **1a** to **5**, and from O to N, when going from **1b** to **1b′**. Since O is more electronegative than N, the former transfer should be favored over the latter, and consequently pathway a occurs preferentially despite the fact that the first step along pathway b may be faster than the corresponding step along pathway a.

This result is similar to that observed when a mixed anhydride such as $CH_3CO_2COCF_3$ is made to react with a nucleophile. It is the fluorocarboxy anion $CF_3CO_2^-$ that is the more stable leaving group, despite the fact that the carbonyl attached to the fluorocarbon group in the more electrophilic center.[4] Similarly, $CF_3SO_2OCOCH_3$ is an outstanding acetylating agent that produces $CF_3SO_3^-$ as the more stable anion.[5]

Although anilines react with acetylanthranil preferentially via pathway a, the primary product **5** is not always isolated as a stable intermediate, even at room temperature. The derivatives of para-substituted anilines and aniline itself precipitate at room temperature as fast as they are formed in a neutral solvent, which serves to prevent cyclodehydration in solution. These amidine salts are usually quite stable as crystalline solids at room temperature. These intermediates, however,

Chart I



are soluble in basic solvents, such as pyridine, so that they are converted rather rapidly, when prepared in these media, to the corresponding quinazolones, especially at somewhat higher temperature. The acetamidine salt derivatives of ortho-substituted anilines, however, are usually not isolated, even when prepared in neutral solvent at room temperature. These derivatives are more soluble and tend to undergo cyclodehydration rapidly in the presence of unreacted amine to give the corresponding quinazolone. The water, liberated in this cyclization, reacts in turn with residual acetylanthranil to give acetylanthranilic acid,[1] which lowers proportionately the yield of products formed with the amine as indicated by somewhat lower yields (ca. 80% instead of ca. 95%) realized with the anilines **f, g, i, j, k,** and **m.** The acetamidine salt derivative of 2,4,6-trimethylaniline was the only ortho-substituted aniline that afforded an isolable intermediate owing to its insolubility. This salt, however, was unstable even in the solid state, since it underwent cyclodehydration within a few months at room temperature.

In view of the ease with which acetamidine derivatives of ortho-substituted anilines undergo cyclodehydration to the stable quinazolone, the observation that anthranilic acid (**2n**) reacts with 1 via pathway b instead of a is all the more noteworthy, since it indicates that this inversion in selectivity is attributable to site differentiation at the moment of attack by the amine rather than manifestations of equilibrium conditions that ensue this event. One suspects immediately that this inversion with anthranilic acid is due to intramolecular hydrogen bonding with the ortho-carboxylic acid group, which decreases the nucleophilicity of the amino group electronically and sterically. It was concluded, however, that this result is not due primarily to simple decreased basicity caused by the electron-withdrawing effect of the electronegative substituent, since the selectivity ratio a/b was not affected either by a meta CF_3 group (aniline, **3g**) or by a para CO_2H group (aniline, **3f**)

Table II. Relevant Ir Absorption Patterns for Product Characterizations

Acetylanthranil (1)	Sharp band at 5.7 μ for semianhydride >C=O Sharp band at 6.1 μ for >C=N-
N-Acetylanthranilic acid (6)	Broad absorption from 3.3 to 4.5 μ for acid OH v sh band at 5.9 μ for acid C=O v sh band at 6.1 μ for amide C=O sh band at 6.6 μ for NH
Acetamidines 5	Broad absorption from 3.3 to 4.2 μ for internal salt Band at ca. 6.3 μ for salt carbonyl
Quinazolones 4	sh band at ca. 5.9 μ for -CONR- carbonyl sh band at ca. 6.1 μ for >C=N-
o-Acetamidobenzamides 3	sh band at ca. 3.0 μ for NH sh band at ca. 6.0 μ for amide C=O Band at ca. 6.5 μ for NH band

despite the fact that higher temperatures were required in both cases to compensate for the decreased reactivity of the nucleophile. In other words, these electronegative substituents on the aromatic amine served only to decrease markedly the overall reaction rate, $k_a + k_b$, but did not affect significantly the relative ratio k_a/k_b, which determines selectivity.

More experimentation is planned to elucidate whether this change in selectivity is indeed due to some form of steric hindrance, as suspected, or to a change in mechanism, both owing to intramolecular hydrogen bonding of the nucleophilic center with the ortho carboxylic acid.

Experimental Section

General Procedure for Reaction of Acetylanthranil with Amines. Acetylanthranil (**1**, 0.03 mol) and an equivalent weight of the amine **2** were dissolved in a neutral solvent (ca. 50 ml, usually benzene or Et_2O), and reaction was allowed to occur at room temperature overnight. If the corresponding acetamidine salt, **5**, separated from solution, it was removed by filtration and washed with fresh solvent. Otherwise the solution was taken directly to dryness at ca. 60 °C by evaporation under vacuum. The residue was leached with dilute aqueous base to remove **5** and/or residual **1**. The alkaline extract was allowed to remain at room temperature overnight to ensure conversion of solvated **5** to insoluble quinazolone, **4**, which was removed conveniently by filtration. Any residual **1** was recovered as *N*-acetylanthranilic acid by acidification of the mother liquor. The residue, from which the acid components were removed by extraction with base, was then extracted with dilute acid to dissolve **4** and/or residual unreacted **2**. Neutralization of this extract with dilute base caused precipitation of any quinazolone, which was collected by filtration and purified further by recrystallization from a suitable solvent, usually methanol. Any residue that resisted sequential extraction with aqueous base and acid was purified further by recrystallization from a suitable solvent, usually heptane or methanol, to give the *o*-acetamidobenzanilide, **3**, in crystalline form.

After the products were separated chemically as described above, their expected structural assignment was verified spectrophotometrically by their ir spectra. The relevant ir absorption patterns which are characteristic for the starting material and all the possible products are given in Table II.

The known chemistry and limited possibilities usually permitted easy differentiation and assignment of structure on the basis of these ir patterns. In cases of doubt, however, the tentative assignment was substantiated by the corresponding NMR data and/or elemental analysis data, which were consistent with the assigned structures. A sample of the acetamidine salt, **5**, was usually converted to the corresponding quinazolone, **4**, by solution in dilute aqueous base at room temperature and subsequent separation of the precipitate by filtration.

Chemical separation of the product mixture and isolation into its acid, base, salt, and neutral components as described above usually accounted for about 95% of the acetylanthranil allowed to react with the amine in question. The melting points and the percent anthranil units isolated as the respective products of reaction with amines **2a–n** are given in Table I.

Registry No.—1, 525-76-8; **2a**, 62-53-3; **2b**, 106-49-0; **2c**, 99-98-9; **2d**, 106-50-3; **2e**, 104-94-9; **2f**, 150-13-0; **2g**, 98-16-8; **2h**, 591-27-5; **2i**, 95-53-4; **2j**, 578-54-1; **2k**, 90-04-0; **2l**, 88-05-1; **2m**, 579-66-8; **2n**, 118-92-3; **3n**, 58426-37-2; **4a**, 2385-23-1; **4b**, 22316-59-2; **4c**, 58426-38-3; **4d**, 27440-42-2; **4e**, 30507-16-5; **4f**, 4005-05-4; **4g**, 1788-98-3; **4h**, 40671-68-9; **4i**, 72-44-6; **4j**, 7432-25-9; **4k**, 4260-28-0; **4l**, 58426-39-4; **4m**, 58426-40-7; **4n**, 4005-06-5; **5a**, 34264-61-4; **5b**, 58426-41-8; **5c**, 58426-42-9; **5d**, 58426-43-0; **5e**, 58426-44-1; **5h**, 58426-45-2; **5l**, 58426-46-3; **6**, 89-52-1.

References and Notes

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(2) (a) G. Heller and G. Fiesselman, *Justus Liebigs Ann. Chem.*, **324**, 134 (1902); (b) R. Anschutz and O. Schmidt, *Ber.*, **35**, 3470 (1902); (c) M. T. Bogert and V. J. Chambers, *J. Am. Chem. Soc.*, **27**, 653 (1905); (d) M. T. Bogert and A. Bender, *ibid.*, **36**, 576 (1914).
(3) A. Katritsky, private communication.
(4) G. A. Olah, "Friedel-Crafts Chemistry", Wiley, New York, N.Y., 1973, p 134.
(5) A. Germain and A. Commeyrais, *J. Chem. Soc., Chem. Commun.*, 1345 (1972).

The Chemistry of Hindered Systems. 2. The Acyloin Reaction—an Approach to Regiospecifically Hydroxylated Tetramethylazacycloheptane Systems

Peter Y. Johnson* and Daniel J. Kerkman

Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218

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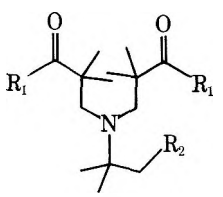
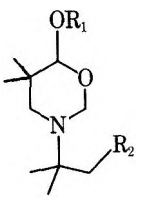
An unusually stable ϵ-lactone, **9**, has been synthesized in high yield by treating mixed animal **7** with 2 equiv of the Grignard reagent generated from ethyl 2-bromoisobutyrate in ether at 0–10 °C. A solvent dependence for this reaction was observed. Reaction of ester lactone **9** under modified acyloin conditions (5 equiv of chlorotrimethylsilane was used as an anion trapping agent) gave acyloin **18** in 68% yield. Infrared studies of the OH stretch region of **18** allowed assignment of several hydrogen bonds and helped to establish possible conformations of **18**. Reduction of **18** with $NaBH_4$ in ethanol at 25 °C was found to occur stereoselectively giving only cis triol **22**. Reduction of **18** with $LiAlH_4$ in refluxing THF gave a 9:1 ratio of cis **22** to trans **24**. The stereochemistry of the triols was established by ^1H NMR techniques employing both achiral and chiral shift reagents and by their ^{13}C NMR spectra. Oxidation of **22** was found to give dialdehyde **5** which was shown to exist in its ϵ-hemiacetal form **25**. In separate experiments, **25** was found to be unstable to prolonged exposure (8 days) to methanol at 25 °C or to heating at 100 °C for 3 h giving, in both cases, aldehyde **26** in high yield. Stereoelectronically controlled reverse Mannich reactions are postulated to explain the latter results. Several molecules, 8 (see ref 6) and **10**, isolated in these studies have been shown to display some anticancer activity.

Our continuing interest in the syntheses[1] and properties[2] of hindered *N-tert*-butyl-3,3′-iminodiesters such as **1** and its aldehyde analogue **2**, which has been shown to undergo a facile rearrangement in alcoholic solvents to give 6-alkoxytetrahydro-1,3-oxazines **3**,[1b,3] a new class of molecules which have been shown to display some anticancer properties,[4] has prompted us to undertake a study of the related hydroxylated systems **4**,[5] **5**, and **6** which we feel might be expected to show



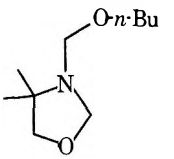
1, R_1 = OEt; R_2 = H
2, R_1 = R_2 = H
4, R_1 = OEt; R_2 = OH
5, R_1 = H; R_2 = OH



3a, R_1 = CH_3; R_2 = H
3b, R_1 = Et; R_2 = H
6, R_1 = CH_3; R_2 = OH

different solubility characteristics. Our efforts directed toward the syntheses of these molecules and studies of their properties will be discussed.

Synthesis of Diester 4 and Lactone 9. Since there are no regiospecific procedures for attaching an OH group to an unactivated alkyl group (e.g., the *tert*-butyl group on diester **1**), a modification of the approach used to synthesize **1**[2] which would allow incorporation of the desired OH group on **4** was devised. Mixed aminal **7** was prepared in 73% yield by treating 2-methyl-2-amino-1-propanol with 2 equiv of formaldehyde and 1 equiv of *n*-butyl alcohol. A minor product, bisoxazolidine **8**, was also isolated from this reaction in ca. 20% yield and was later synthesized by an independent route.[6]



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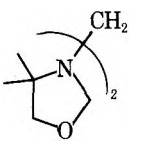

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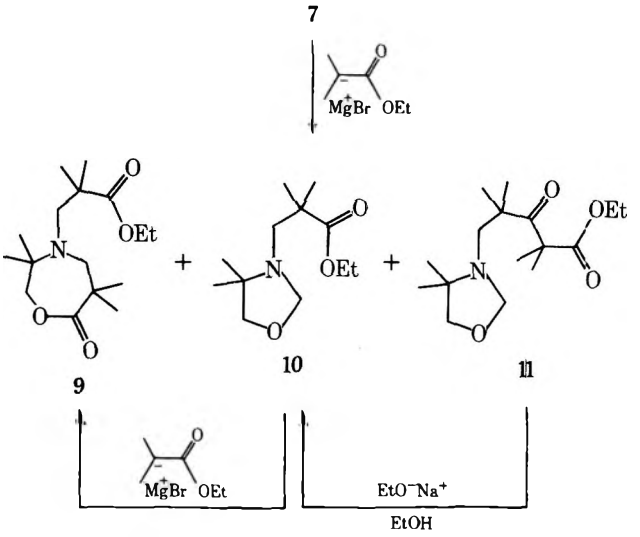
Treatment of aminal **7** (Scheme I) with 2 equiv of the Grignard reagent generated from ethyl 2-bromoisobutyrate under mild conditions in anhydrous ether gave, after normal acid–base work-up, a crude material which did not have the properties expected for the desired diester **4**, but which was identified after purification as ethyl *N*-2-(1-hydroxy-2-methylpropyl)-3,3′-imino-2,2,2′,2′-tetramethyldipropionate ϵ-lactone (**9**). An oil, which was identified as monoadduct **10**, was also isolated from this reaction along with small amounts of an isobutyrisobutyrate adduct **11**. The yields of **9** (35–62%) and **10** (10–35%) varied depending on the scale of the reaction and stirring efficiency since insoluble magnesium salts were formed during this reaction. When THF was used as the solvent in this reaction isobutyrisobutyrate adduct **11** and monoadduct **10** were isolated in 57 and 26% yields, respectively. No lactone was recovered in this case.

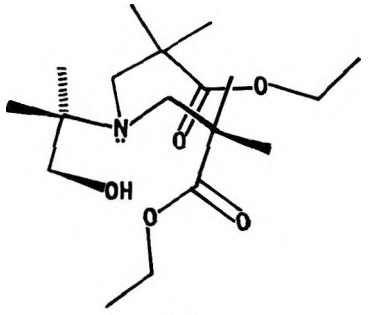
The overall recovery of lactone **9** from these reactions could be increased since: (1) diadduct **11** was found to undergo a reverse Claisen reaction to give **10** in high yield when treated with sodium ethoxide in refluxing ethanol; and (2) monoad-

Scheme I



duct **10** could be converted to lactone **9** in 50–60% yields when treated with 1 equiv of the ethyl isobutyrate Grignard reagent in ether at 0–10 °C. These reactions are shown in Scheme I. In the course of our studies it was noted that when the Grignard reaction was quenched at 0 °C with ice water and the aqueous phase extracted quickly with cold ether, the primary products, as determined by ^{1}H NMR analysis, were diester **4** rather than lactone **9**[5] and oxazolidine **10** and that diester **4** could be isolated in moderate yield and good purity by manipulation of the work-up and purification procedures related to the Grignard reaction (see Experimental Section). All attempts to purify **4** (e.g., GLC, TLC, or column chromatography using silicic acid) resulted in its conversion to **9**. Preliminary attempts to protect the OH group on **4** (e.g., via acylation) also resulted in its conversion to lactone **9**.

We feel that the ready lactonization of **4** occurs as a result of the close proximity of the hydroxymethyl OH group with at least one of the two ester groups of **4** and that this close proximity is due to restricted conformational preferences (see **12**) related to the hindered character of this molecule.[7] This



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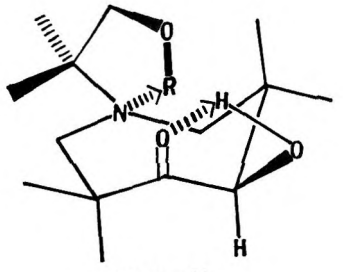
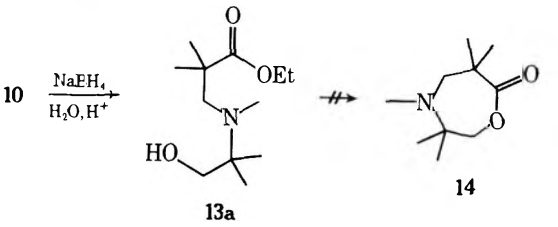
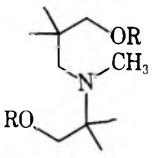


21, R = H
23, R = AlH_3

contention is supported in part by the observation that ester alcohol **13a**, which was synthesized by careful $NaBH_4$ reduction of **10** in aqueous acid (pH ~3) and which can readily exist in a linear conformation, could not be converted to ε-lactone **14** using conditions which readily converted **4** to **9** (eq 1).

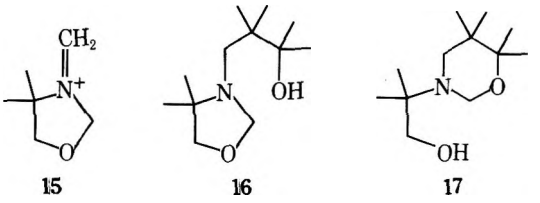


When **10** was treated with $NaBH_4$ in THF no reaction was observed; however, when a catalytic amount of zinc chloride was added to the reaction mixture, complete reduction of **10** occurred to give diol **13b** which was characterized as its diacetate **13c**.



13b, R = H
13c, R = Ac

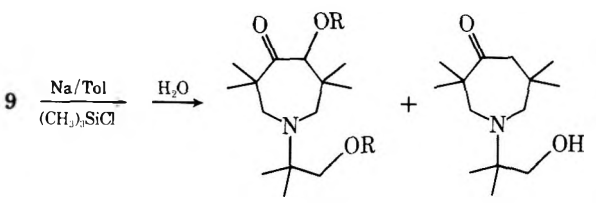
With regard to the formation of **10** and **4** (**9**), we feel our results indicate that initial reaction of the Grignard reagent with aminal **7** takes place at the exocyclic methylene carbon after Lewis acid catalyzed formation of immonium ion **15**. The



15 **16** **17**

fact that reaction of **10** with 4 equiv of methyllithium in THF at 35 °C gave only products resulting from attack at the ester carbonyl, namely a 4:1 mixture of oxazolidine **16** and tetrahydro-1,3-oxazine **17**, supports the intermediacy of a species such as **15** as opposed to direct nucleophilic attack on **7** by the Grignard reagent. It is interesting to note that treatment of this mixture of alcohols with zinc chloride in refluxing THF for 4 h resulted in the clean conversion of **16** to the thermodynamically more stable **17**.

Acyloin Reaction of Lactone 9. A Synthesis of 5. Treatment of ester lactone **9** under acyloin conditions[8] resulted in the formation of **18** in yields ranging from 35 to 62% depending on the reaction time and the scale of the reaction. The addition of 5 equiv of chlorotrimethylsilane[9] to this acyloin reaction seemed to consistently improve the isolated yield of **18** (e.g., 68% on a 0.01-mol scale). This modification, which would be expected to quench sodium ethoxide formed during the reaction, was tried when it was noticed that lactone **9** underwent complete decomposition when heated in the presence of sodium ethoxide in ethanol for extended periods. Conversion of **18** to diacetate **19** in nearly quantitative yield



18, R = H
19, R = Ac

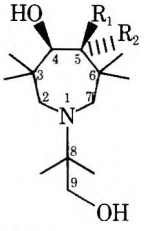
20

confirmed the existence of two OH groups in this molecule. A minor product, ketone **20**, was also isolated from these acyloin reactions in variable yields (eq 2).

Ketol **18** was characterized by its spectra, showning a molecular ion at *m/e* 257 in its mass spectrum and the expected six different methyl signals in both its ^1H and ^{13}C NMR spectra. The existence of a carbonyl band at 1700 cm^{-1} in its infrared spectrum indicated that transannular interactions resulting in hemiacetal formation are not important for **18**[10a] as has been the case for products isolated from the acyloin reaction of other ester lactone substrates[11] as well as other molecules in this series (i.e., **25**).

Careful studies of the OH (and C=O) stretch region of the infrared spectrum of **18**, obtained at various dilutions, and studies of models suggest that the primary hydroxy group and the carbonyl oxygen are in close proximity even though they are separated by six atoms, but do not indicate a transannular nine-membered ring hydrogen bond to the carbonyl.[10b] Specifically, absorptions at 3640 (free OH), 3515, and 3470 cm^{-1} indicate the presence of two associated OH groups having $\Delta\nu$'s of 125 and 170 cm^{-1}, respectively. Comparisons with model systems such as $HO(CH_2)_2N(CH_3)_2$, which shows a $\Delta\nu$ of 138 cm^{-1},[12a] and various α-ketols,[12] which show $\Delta\nu$'s ranging from 180 cm^{-1} (O=C–C–O dihedral angle $\approx 0°$) to ca. 10 cm^{-1} (O=C–C–O dihedral angle $\geq 120°$), suggest both a five-membered ring OH–NR_2 hydrogen bond and an α-ketol hydrogen bond with a O=C–C–O dihedral angle near 0° for **18**. An appropriate cycloheptanoid half-twist boat, half-chair conformation such as **21**, which we feel constitutes the preferred ground-state geometry for these hindered azacycloheptanone systems,[1b] would fit the infrared data while many other conformations can be ruled out because of their large O=C–C–O dihedral angle or CH_3–CH_3 interactions.

While reduction of **18** with $NaBH_4$ in ethanol was expected to parallel that of the *N-tert*-butyl analogue[1b] and give mainly cis triol **22**, it was hoped that reduction of **18** with $LiAlH_4$



22, R_1 = OH; R_2 = H

24, R_1 = H; R_2 = OH

might occur, at least to some extent, via delivery of hydride in a transannular manner from alumunate ester **23**[13] leading to a predominance of trans triol **24**. The reaction of **18** with $NaBH_4$ was found to be stereoselective giving only cis triol in contrast to its *N-tert*-butyl analogue, which gave an 8/2 mixture of cis and trans diols, respectively, under similar conditions.[1b] The reaction of acyloin **18** with $LiAlH_4$ in refluxing THF gave a 9/1 mixture of cis to trans triols. These results have led us to conclude that only steric factors related to the hydroxylated *tert*-butyl group are important in reductions of acyloin **18**.

The triols were separated by column chromatography using silicic acid with hexane–ether elution and were identified by ^1H and ^{13}C NMR techniques. Triol **22**, a meso compound, which was eluted after triol **24**, displayed a singlet at δ 1.02 ($CDCl_3$) integrating for 18 H in its ^1H NMR spectrum indicating that the protons on all six methyl groups of this molecule are isochronous. When the ^1H NMR spectrum was obtained in the presence of 0.2 or 0.4 equiv of the achiral shift reagent $Eu(fod)_3$, three signals of nearly equal intensity appeared indicating the presence of three pairs of enantiotopic

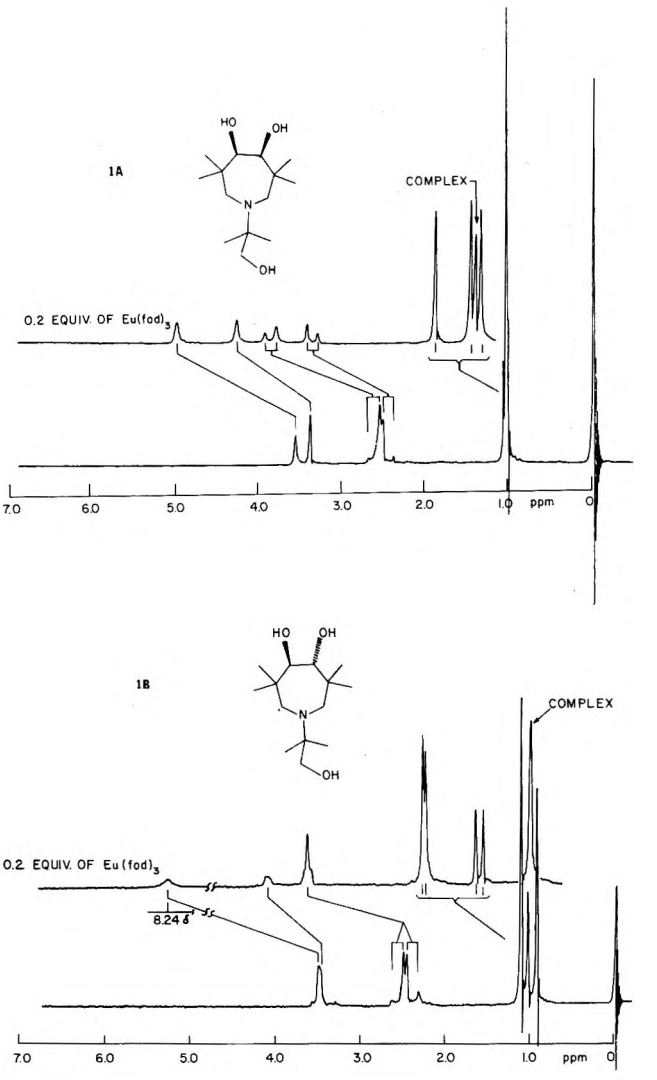


Figure 1. ^1H NMR spectra of triols **22** and **24**: A, **22** (ca. 5% in $CDCl_3$) with insert showing the ^1H NMR spectrum obtained in the presence of 0.2 equiv of $Eu(fod)_3$; B, **24** (ca. 5% in $CDCl_3$) with insert showing the ^1H NMR spectrum obtained in the presence of 0.2 equiv of $Eu(fod)_3$.

methyl groups. In the presence of chiral shift reagent [i.e., 0.4 equiv of $Eu(facam)_3$] the methyl groups became diastereotopic owing to the formation of a "pseudocontact" enantiomer[1b] and six signals of near equal intensity appeared.

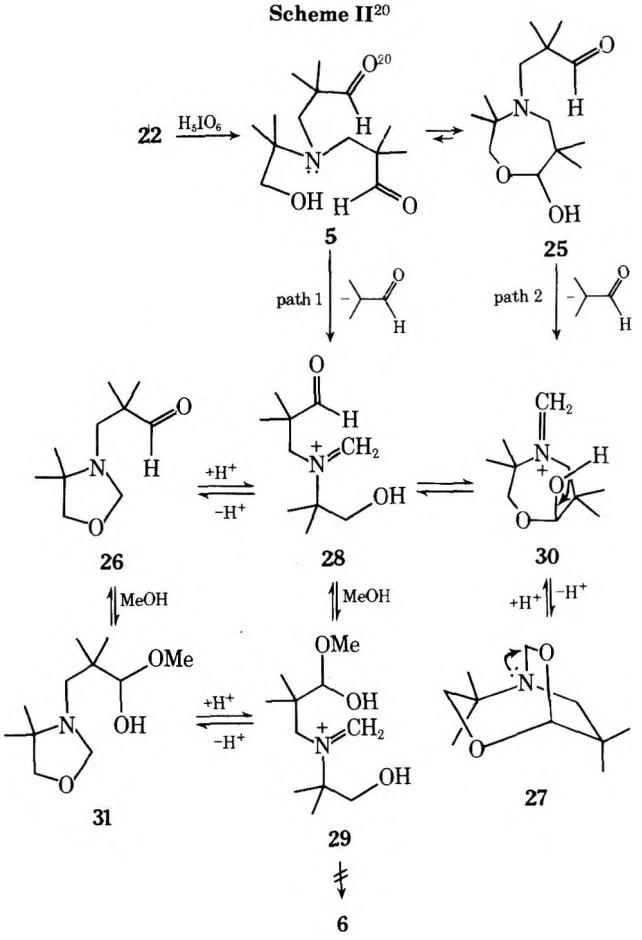
The ^1H NMR spectrum of triol **24** ($CDCl_3$) showed three signals in the methyl region of the spectrum occurring at δ 0.91 (6 H), 1.04 (3 H), and 1.12 (9 H). Because the signal at δ 1.12 appeared to have a shoulder at δ 1.13, the spectrum was obtained in the presence of $Eu(fod)_3$ which allowed resolution of the methyl region of the spectrum and showed two signals integrating for 6 H and two signals integrating for 3 H. This is the pattern one would expect for a trans 3,3,6,6-tetramethyl-1-azacycloheptane-4,5-diol moiety which possesses C_2 symmetry as a result of rapid inversion, rotation processes occurring at nitrogen and which is attached by a bond lying on the C_2 axis to a prochiral carbon[14] possessing two methyl groups. The two methyl groups at C-3 (see **24** for the numbering system) are diastereotopic as are the two at C-6, but since the pro-*R* methyl at C-3 and the pro-*R* methyl at C-6 are homotopic for each enantiomer at ambient temperatures as are the respective pro-*S* methyl groups, only two signals integrating for 6 H each are expected for the tetramethylazacycloheptane moiety. Because of the chirality associated with a group having C_2 symmetry, the two methyl groups on the exocyclic prochiral carbon, C-8, will be diastereotopic. This

accounts for the observed patterns.[15] The ^1H NMR spectra of **22** and **24**, including Eu(fod)$_3$ inserts, are shown in Figure 1.

The cis and trans assignments for **22** and **24** were further confirmed using ^{13}C NMR.[16] Triol **22** showed signals for the eight different carbons expected for this meso compound, while the trans isomer showed signals for nine different carbons reflecting the diastereotopic character of the methyl carbons attached to the exocyclic prochiral center at C-8 of **24**.

Oxidation of triol **22** (Scheme II) using 1 equiv of paraperiodic acid in either aqueous acid (pH ~3) or methanol at ambient temperatures led, after workup, to the same crude semisolid material which did not have the properties expected for dialdehyde **5** but which was identified after purification by careful sublimation (pot temperature ca. 50 °C) as ϵ-hemiacetal **25**[16] (mp 89–90 °C). Attempts to purify crude **25** by distillation led to the formation of a mixture of **25** and a new product which was identified as oxazolidine **26**. Subsequently it has been found that heating **25** in refluxing dioxane for 4 h leads to its quantitative conversion to **26**.

Scheme II[20]



Unlike *N-tert*-butyl dialdehyde **2** which decomposed to give tetrahydro-1,3-oxazine **3a** when stirred in methanol at 25 °C for 15 h, anomer **25**, which might be expected to be in equilibrium with its dialdehyde form **5** in polar solvents such as methanol, did not break down in this solvent to form either the desired 6-methoxytetrahydro-1,3-oxazine **6** or a hoped for [3.2.2]bicyclotetrahydro-1,3-oxazine **27**, which might have resulted from intramolecular capture of the hemiacetal OH group by the incipient immonium ion[17] (see Scheme II, path 2), but rather broke down over several days to give good yields of **26**. Because of the previously demonstrated preference for the formation of six-membered rings over five-membered rings in related systems (e.g., **16** → **17**), efforts were made to synthesize **6** by equilibrating the hemiacetal of **26** (i.e., **31**) generated in situ in the presence of methanol containing a catalytic amount of zinc chloride. While the zinc chloride caused the slow decomposition of **26**, no evidence for the formation of **6** was obtained upon examination of the ^1H NMR spectrum of the crude reaction mixture. The above reactions and possible intermediates involved in the formation of **26** are summarized in Scheme II. We feel that **5** and **25** are in an equilibrium which favors **25** under normal conditions and that formation of **26** results indirectly from intermediate ion **28**[20] (formed via path 1 or path 2). Experimental evidence indicates that immonium ions **28** and **30** may be formed via a reverse Mannich reaction[18] which involves the stereoelectronically controlled[19] loss of isobutyraldehyde from amines **5** and **25**, respectively.

While the lack of direct capture of the OH group on **30** to give the bicyclo system **27** could be explained by the overall lack of importance of path 2 (Scheme II) or by the strained nature of the product which might, if formed, revert back to **30** under the reaction conditions, our inability to isolate **6**, considering the viability of intermediate **29**, is harder to understand. Further work on the chemistry and properties of these hindered amines is in progress.

Experimental Section

Melting points were taken in capillary tubes on a Thomas-Hoover Unimelt and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 457 A spectrometer. The ^1H NMR spectra were taken either on a Varian A-60 spectrometer or on a Perkin-Elmer JEOL MH-100 spectrometer and are reported in parts per million downfield from tetramethylsilane. The ^{13}C NMR spectra were taken on a Varian CFT-20 spectrometer and are reported in parts per million downfield from tetramethylsilane. The abbreviations s, singlet; d, doublet; t, triplet; q, quartet refer to the multiplicity of the absorption in an off-resonance decoupled spectrum. Mass spectra were determined on a Perkin-Elmer Hitachi RMU-6D spectrometer. Ultraviolet spectra were taken on a Cary 14 recording spectrophotometer. Gas chromatography was carried out using programmed temperature control on a Hewlett-Packard 5750 B instrument equipped with 8- and 10-ft stainless steel columns packed with SE-30 on 80–100 mesh Chromosorb P. Mallinckrodt AR 100 mesh silicic acid was used for all column chromatography. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

***N*-*n*-Butoxymethyl-4,4-dimethyl-1,3-oxazolidine (7).** To a mixture of 74 g (1.0 mol) of 1-butanol, 60 g (2.0 mol) of paraformaldehyde, and 400 ml of benzene was added dropwise 89 g (1.0 mol) of 2-amino-2-methyl-1-propanol. The mixture was brought to reflux and water removed as an azeotrope using a Dean-Stark trap. After removal of the theoretical amount of water, the solvents were distilled off at 100 mm pressure and finally the crude oil remaining was distilled under high vacuum to give 136 g (73%) of pure **7** as a clear liquid: bp 59–60 °C (0.3 mm); ir (CCl_4) no C=O; ^1H NMR (CCl_4) δ 0.91 (t, 3), 1.17 (s, 6), 1.44 (m, 4), 3.35 (t, 2), 3.48 (s, 2), 4.19 (s, 2), 4.57 (s, 2); mass spectrum (70 eV) *m/e* (rel intensity) 187 (trace, M^+), 114 (37), 70 (39), 57 (70), 56 (36), 55 (23), 42 (100), and 41 (55).

Bisoxazolidine **8** was also isolated as a high-boiling oil in ca. 20% yield from this reaction (see below).

***N,N'*-Methylenebis(4,4-dimethyl-1,3-oxazolidine) (8).** To a refluxing mixture of 1.29 g (0.043 mol) of trioxane and 200 ml of benzene was added dropwise 2.54 g (0.029 mol) of 2-amino-2-methyl-1-propanol. After removal of water and workup as described for **7**, **8** was isolated by distillation in 35% yield: bp 80–83 °C (0.3 mm); ir (CCl_4) no C=O; ^1H NMR (CCl_4) δ 1.09 (s, 12), 3.39 (s, 2), 3.52 (s, 4), 4.41 (s, 4).

Reactions of 7. A. Diethyl *N*-2-(1-Hydroxy-2-methylpropyl)-3,3'-imino-2,2,2',2'-tetramethyldipropionate (4). Into a flame-dried three-neck Morton flask equipped with an overhead stirrer, addition funnel, and condenser was added 12.15 g (0.5 mol) of clean magnesium turnings and 50 ml of dry ether. To the stirring mixture, which was under N_2 and cooled to 10–20 °C, was added, over several hours, 82.0 g (0.4 mol) of ethyl 2-bromoisobutyrate in 200 ml of ether. After complete formation of the Grignard reagent (determined by GLC analysis), 37.4 g (0.2 mol) of aminal **7** in 300 ml of ether was added to

the flask over several hours (stirring becomes difficult as 7 is added) and the reaction mixture was stirred for an additional 1 h at 10–20 °C. After the mixture was cooled to 0 °C, ice water was added and the mixture extracted three times with cold ether. The ether was dried over K_2CO_3 and evaporated under vacuum to give a crude oil which was shown by ^1H NMR analysis to contain monoadduct **10** and diester **4**. The crude mixture was rapidly distilled to give **10** (ca. 20% yield, see below) and a high-boiling fraction which was shown to be a mixture of **4** and lactone **9**. The high-boiling mixture was dissolved in a small amount of hexane and allowed to cool at −10 °C for 24 h causing **9** to precipitate. Lactone **9** was removed from the hexane mixture by vacuum filtration and the hexane solvent removed from the mother liquor under high vacuum to give an oil which was not further purified but was characterized as diester **4**: yield ca. 50%; bp 123–127 °C (0.1 mm) with decomposition to **9**; ir ($CHCl_3$) 3500, 2960, 1720, 1260, 1145, and 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (s, 6), 1.20 (s, 12), 1.27 (t, 6, J = 7 Hz), 2.82 (s, 4), 2.91 (br s, 1, absent in D_2O), 3.32 (s, 2), and 4.12 (q, 4, J = 7 Hz).

Anal. Calcd for $C_{18}H_{35}NO_5$: C, 62.58; H, 10.21. Found: C, 64.85; H, 10.45.

Reactions of 7. B. Ethyl *N*-2(1-Hydroxy-2-methylpropyl)-3,3′-imino-2,2,2′,2′-tetramethyldipropionate ε-Lactone (9). The Grignard reaction was run as described above to obtain a crude material which was subjected to an acid–base work-up. The crude amines were added to a flask containing ethanol in which a trace of sodium had been dissolved and were heated for 0.5 h. After removal of the ethanol in vacuo and an acid–base work-up the crude material was distilled to give 15.5 g (34%) of **10** (see below) and 31 g (52%) of lactone **9**.

For **9**: bp 133–138 °C (0.2 mm); mp (hexane) 76–77 °C; ir ($CHCl_3$) 2978, 1725, 1467, 1392, 1370, and 1140 cm^{-1}; ir (CCl_4) 1730 and 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 25 °C[5]) δ 1.06 (s, 6), 1.19 (s, 6), 1.27 (s, 6), 1.28 (t, 3, J = 7 Hz), 2.57 (s, 2), 2.71 (s, 2), 3.99 (s, 2), and 4.13 (q, 2, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 14.01 (q), 19.99 (broad, q), 24.58 (q), 26.81 (q), 43.22 (s), 44.83 (s), 57.32 (s), 57.84 (t), 58.34 (t), 60.49 (t), 74.07 (t), 177.16 (s), 177.53 (s); mass spectrum (70 eV) m/e (rel intensity) 299 (6, M^+), 284 (1), 198 (6), 184 (100), 112 (43), 84 (83), 70 (60), and 55 (25) with metastable peaks at m/e 113.0 ($184^2/299$), 68.0 ($112^2/184$), and 63.2 ($84^2/112$).

Anal. Calcd for $C_{16}H_{29}NO_4$: C, 64.18; H, 9.76; N, 4.68. Found: C, 64.51; H, 9.72; N, 4.79.

Reactions of 7. C. Ethyl 2,2-Dimethyl-3-[*N*-(4,4-dimethyl-1,3-oxazolidine)]propionate (10) and Ethyl 2,2,4,4-Tetramethyl-5-[*N*-(4,4-dimethyl-1,3-oxazolidine)]-3-oxopentanoate (11). The Grignard reaction was run as described above but THF was used as the solvent for the reaction in place of ether. Acid–base work-up and purification by distillation gave 12.5 g (26%) of mono adduct **10** and 34 g (57%) of diadduct **11**.

For **10**: bp 80–81 °C (0.1 mm); ir (CCl_4) 2970, 2870, 1735, 1475, 1273, 1250, 1145, 1100, 1030, and 947 cm^{-1}; ^1H NMR (CCl_4) δ 1.01 (s, 6), 1.12 (s, 6), 1.22 (t, 3, J = 7 Hz), 2.58 (s, 2), 3.49 (s, 2), 4.08 (q, 2, J = 7 Hz), 4.29 (s, 2); mass spectrum (70 eV) m/e (rel intensity) 229 (1, M^+), 114 (100), and 42 (85).

Anal. Calcd for $C_{12}H_{23}NO_3$: C, 62.85; H, 10.11; N, 6.11. Found: C, 62.80; H, 10.07; N, 6.18.

For **11**: bp 114–118 °C (0.2 mm); ir (CCl_4) 2970, 2870, 1742, 1695, 1465, 1260, and 1145 cm^{-1}; ^1H NMR (CCl_4) δ 0.98 (s, 6), 1.12 (s, 6), 1.25 (t, 3, J = 7 Hz), 1.30 (s, 6), 2.52 (s, 2), 3.42 (s, 2), 4.12 (q, 2, J = 7 Hz), 4.21 (s, 2); mass spectrum (70 eV) m/e (rel intensity) 299 (trace, M^+), 114 (100), and 42 (75).

Anal. Calcd for $C_{16}H_{29}NO_4$: C, 64.18; H, 9.76. Found: C, 63.96; H, 9.76.

Conversion of 11 to 10. Diadduct **11**, 2 g (6.7 mmol), was refluxed under N_2 in 150 ml of ethanol in which 0.1 g of sodium had been previously dissolved. Solvent was removed steadily from the flask via a Dean-Stark trap until the volume of solvent was near 50 ml (ca. 20 h). The remaining solvent was removed in vacuo and the crude residue extracted with water–ether. The ether layer was dried with K_2CO_3 and evaporated to give an oil which was distilled to give 1.07 g (70%) of pure **10**.

Grignard Reaction of 10. These reactions were run in ether solvents using 1 equiv each of magnesium, ethyl 2-bromoisobutyrate, and monoadduct **10** as described above for the reactions of **7**. The products isolated, **4** or **9** (50–60%), depended on the workup employed (see above).

Reduction of 10. Ethyl 6-Hydroxy-2,2,4,5,5-pentamethyl-4-azahexanoate (13a). To a mixture of 0.98 g (4.3 mmol) of **10** in 25 ml of ethanol and enough 6 N HCl to obtain a pH of ca. 3 was added dropwise, over 1 h, 0.17 g (4.5 mmol) of $NaBH_4$ dissolved in water containing a trace of base as a stabilizer. The pH of the reaction mixture was maintained at ca. 3 with 6 N HCl as the reaction progressed. After being allowed to stir for 15 min the reaction was quenched with cold aqueous KOH and the ethanol removed in vacuo. Water–ether extraction of the crude residue followed by evaporation of the ether and distillation of the organic material gave 0.65 g (65%) of ester **13a**: bp 92–95 °C (0.2 mm); ir ($CHCl_3$) 3640, 3425, 2920, 1720, 1265, 1145, and 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (s, 6), 1.17 (s, 6), 1.23 (t, 3, J = 7 Hz), 2.14 (s, 3), 2.57 (s, 2), 3.2 (br s, 1, absent D_2O), 3.28 (s, 2), and 4.06 (q, 2, J = 7 Hz); mass spectrum (70 eV) m/e (rel intensity) 231 (none, M^+), 213 (1, $-H_2O$), 185 (2, −HOEt), 98 (100), and 44 (40). Reduction of **10** using $NaBH_4$ in THF containing zinc chloride or using $LiAlH_4$ in THF resulted in near quantitative formation of diol **13b** which was characterized as its diacetate **13c** synthesized by treating **13b** with acetic anhydride–pyridine.

For **13b**: bp 90–91 °C (0.2 mm); ir ($CHCl_3$) 3600, 3380, 2920, and 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (s, 6), 1.02 (s, 6), 2.28 (s, 3), 2.42 (s, 2), 3.39 (s, 2), 3.42 (s, 2), and 4.6 (br s, 2, absent D_2O).

For **13c**: bp 97–98 °C (0.2 mm); ir ($CHCl_3$) 2950, 1735, 1725, 1235, and 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (s, 6), 1.03 (s, 6), 2.04 (s, 6), 2.25 (s, 3), 2.30 (s, 2), 3.80 (s, 2), and 3.90 (s, 2); mass spectrum (70 eV) m/e (rel intensity) 273 (trace, M^+), 98 (100), and 43 (27).

Reaction of 10 with Methyllithium. 2,3,3-Trimethyl-4-[*N*-(4,4-dimethyl-1,3-oxazolidine)]-2-butanol (16) and 2-Methyl-2-[*N*-(5,5,6,6-tetramethyltetrahydro-1,3-oxazine)]-1-propanol (17). To 0.38 g (1.65 mmol) of oxazolidine **10** dissolved in 25 ml of dry THF under N_2 at 35 °C was added 5.05 ml (6.55 mmol) of 1.3 M methyllithium in ether. The mixture was heated for 40 min, cooled to 25 °C, and extracted with water–ether. The ether layer was dried over K_2CO_3 and evaporated to give 0.32 g (90%) of a 4:1 mixture of **16** to **17** as judged by ^1H NMR.

Treatment of this mixture (0.30 g, 1.4 mmol) with a catalytic amount of zinc chloride in 25 ml of refluxing THF for 3 h under N_2 allowed the isolation, after acid–base work-up, of 0.27 g (90%) of oxazine **17**.

For **16**: ir ($CHCl_3$) 3645, 3280, no C=O, and 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (s, 6), 1.16 (s, 6), 1.21 (s, 6), 2.59 (s, 2), 3.58 (s, 2), and 4.52 (s, 2); mass spectrum (70 eV) m/e (rel intensity) 215 (1, M^+).

For **17**: bp 76–77 °C (0.2 mm); ir ($CHCl_3$) 3645, 3280, no C=O, and 1085 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (s, 6), 1.05 (s, 6), 1.18 (s, 6), 2.45 (s, 2), 3.33 (s, 2), and 4.32 (s, 2); mass spectrum (70 eV) m/e (rel intensity) 215 (1, M^+).

Anal. Calcd for $C_{12}H_{25}NO_2$: C, 66.93; H, 11.70. Found: C, 66.75; H, 11.66.

Acyloin Reaction of Lactone 9. *N*-2-(1-Hydroxy-2-methylpropyl)-3,3,6,6-tetramethyl-1-azacycloheptan-4-on-5-ol (18). Into a dried three-neck 500-ml Morton flask equipped with an overhead stirrer, addition funnel, and condenser was added 200 ml of dried toluene and 1.3 g (0.057 mol) of sodium metal. The toluene was brought to reflux and the sodium converted to a fine sand in a N_2 atmosphere using high-speed stirring. Lactone **9** (3.53 g, 0.012 mol) in 50 ml of toluene and 10 ml (0.08 mol) of chlorotrimethylsilane were added simultaneously, but from separate addition funnels (one was placed on top of the condenser) over 0.5 h. After the reaction mixture was allowed to reflux for 4 h, it was cooled to 0 °C and quenched with 10% aqueous NH_4Cl. The pH of the mixture was adjusted to 14 using KOH and the aqueous layer extracted several times with ether which was evaporated in vacuo to give a crude material. The crude mixture was stirred in methanol containing 10% aqueous HCl for 3 h in order to hydrolyze any sililated oxygen groups. Acid–base work-up gave 2.06 g (68%) of ketol **18**: mp (sublimed) 67–69 °C; ir ($CHCl_3$) 3640, 3515, 3470, 2970, 2865, 1700, 1470, 1400, 1380, 1362, 1210, 1050, and 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.71 (s, 3), 0.99 (s, 3), 1.03 (s, 3), 1.06 (s, 3), 1.13 (s, 3), 1.28 (s, 3), 2.53 (br s, 1, absent D_2O), 2.61 (AB, 2, J = 14 Hz), 2.73 (AB, 2, J = 16 Hz), 3.41 (AB, 2, J = 11 Hz), 3.82 (d, 1, J = 6 Hz, absent in D_2O), and 4.23 (d, 1, J = 6 Hz, s in D_2O); ^{13}C NMR ($CDCl_3$) δ 19.52 (q), 20.38 (q), 23.18 (q), 24.21 (q), 25.75 (q), 25.87 (q), 40.00 (s), 47.04 (s), 58.87 (s), 59.60 (t), 64.06 (t), 68.80 (t), 79.40 (d), and 217.38 (s); mass spectrum (70 eV) m/e (rel intensity) 257 (2, M^+), 255 (3), 239 (4), 226 (100), 198 (25), 84 (20), 83 (20), 70 (33), 57 (50), and 43 (40); uv λ_{max} (EtOH) 290 nm (ϵ 53), 248 (shoulder, 200).

Anal. Calcd for $C_{14}H_{27}NO_3$: C, 65.33; H, 10.58. Found: C, 64.94; H, 10.49.

When this reaction was run on a larger scale the yield of **18** generally decreased. When run in the absence of chlorotrimethylsilane the yields of **18** varied from 35 to 62%. A minor product, which was observed in as high as 5% yields and which could be isolated pure by column chromatography using silicic acid with hexane–ether elution, was identified as *N*-2-(1-hydroxy-2-methylpropyl)-3,3,6,6-tetramethyl-1-azacycloheptan-4-one (**20**): mp (sublimation) 78–80 °C; ir ($CHCl_3$) 3500, 2965, 2870, 1696, and 1048 cm^{-1}; ir (CCl_4) 3640, 3515,

and 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (s, 6), 1.00 (s, 12), 2.32 (br s, 1, absent D_2O), 2.39 (s, 2), 2.47 (s, 2), 2.71 (s, 2), 3.34 (br s, 2, sharp in D_2O, CH_2OH); ^{13}C NMR ($CDCl_3$) δ 22.16 (q), 23.98 (q), 27.73 (q), 34.43 (s), 48.77 (s), 52.19 (t), 59.01 (s), 61.09 (t), 65.39 (t), 68.91 (t), 215.46 (s); mass spectrum (70 eV) *m/e* (rel intensity) 241 (3, M^+), 223 (15), 210 (30), 198 (18), 182 (100), 84 (45), 70 (40), 55 (50), 43 (70), and 41 (70).

***N*-2-(1-Acetoxy-2-methylpropyl)-3,3,6,6-tetramethyl-5-acetoxy-1-azacycloheptan-4-one (19).** Diacetate **19** was synthesized by refluxing 0.5 g of ketol **18** in a 1/1 mixture of acetic anhydride–acetic acid (6 ml total) for 3 h. Acid–base workup gave 0.60 g (90%) of **19**: mp (sublimed) 76–79 °C; ir ($CHCl_3$) 2965, 1740, 1725, 1245, and 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (s, 3), 0.97 (s, 3), 1.06 (s, 3), 1.12 (s, 6), 1.17 (s, 3), 2.06 (s, 3), 2.10 (s, 3), 2.68 (AB, 2, J = 13 Hz), 2.87 (AB, 2, J = 14 Hz), 3.98 (s, 2), and 5.11 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 341 (trace, M^+), 268 (100), 222 (32), and 43 (80); uv λ_{max} (EtOH) 290 nm (ϵ 55), 244 (shoulder, 270).

Anal. Calcd for $C_{18}H_{31}NO_5$: C, 63.31; H, 9.15. Found: C, 63.59; H, 9.27.

Reduction of 18. *cis*-*N*-2-(1-Hydroxy-2-methylpropyl)-3,3,6,6-tetramethyl-1-azacycloheptane-4,5-diol (22) and Trans Triol 24. A mixture of 0.937 g (3.64 mmol) of ketol **18** and excess $NaBH_4$ was stirred at 25 °C in ethanol for 19 h. After removal of the ethanol in vacuo and acid–base workup, a crude solid was isolated. Analysis by GLC, TLC, and ^1H NMR indicated that only one diastereomer was obtained. Sublimation of the solid gave 0.836 g (85%) of pure cis **22**: mp 136–137 °C; ir ($CHCl_3$) 3595, 3440, 2940, 2875, and 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (s, 18), 2.56 (AB, 4, J = 14 Hz), 3.03 (br s, 3, absent in D_2O), 3.41 (s, 2), and 3.59 (s, 2); ^{13}C NMR ($CDCl_3$) δ 21.96 (q), 25.37 (q), 28.07 (q), 38.17 (s), 58.79 (s), 60.88 (t), 68.99 (t), and 81.12 (d); mass spectrum (70 eV) *m/e* (rel intensity) 259 (trace, M^+) and 228 (100).

Anal. Calcd for $C_{14}H_{29}NO_3$: C, 64.82; H, 11.27. Found: C, 65.08; H, 11.28.

When **18** was reduced by adding it to a refluxing mixture of $LiAlH_4$ in THF a ca. 9:1 mixture of cis **22** and trans **24** triols was obtained. These could be separated by careful column chromatography using silicic acid with hexane–ether–ethanol elution. Triol **24** was eluted first.

For **24**: mp (sublimed) 161–163 °C; ir ($CHCl_3$), 3635, 3515, 2950, 1035, and 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (s, 6), 1.04 (s, 3), 1.12 (s, 9), 2.48 (AB, 4, J = 13 Hz), 2.36 (br s, 3, absent in D_2O), 3.44 (br s, 2), and 3.48 (br s, 2); ^{13}C NMR ($CDCl_3$) δ 19.93 (q), 20.89 (q), 23.06 (q), 27.65 (q), 37.47 (s), 58.84 (s), 63.99 (t), 69.18 (t), and 74.48 (d); mass spectrum (70 eV) *m/e* (rel intensity) 259 (1, M^+), and 228 (100).

Anal. Calcd for $C_{14}H_{29}NO_3$: C, 64.82; H, 11.27. Found: C, 64.87; H, 11.18.

Oxidation of 22. *N*-2-(1-Hydroxy-2-methylpropyl)-3,3′-imino-2,2,2′,2′-tetramethyldipropanal ϵ-Hemiacetal (25). Triol **22** (3.80 g, 0.0147 mol) and paraperiodic acid (3.60 g, 0.015 mol) were stirred in methanol solvent for 24 h at 25 °C. The methanol was removed in vacuo and the residue was extracted with 10% aqueous K_2CO_3–ether. The ether layer was dried with K_2CO_3 and evaporated to give 1.8 g of a crude semisolid. Purification by sublimation (pot temperature ≤50 °C) gave 1.7 g (44%) of pure **25**: mp 89–90 °C; ir ($CHCl_3$) 3680, 3400, 2960, 2810, 2700, 1720, 1468, 1365, and 1085 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (s, 3), 0.94 (s, 3), 0.98 (s, 3), 1.06 (s, 6), 1.14 (s, 3), 2.16 (d, 2, J = 14 Hz), 2.60 (AB, 2, J = 14 Hz), 2.62 (d, 2, J = 14 Hz), 3.26 (d, 2, J = 14 Hz), 3.40 (br s, 1, absent D_2O), 3.82 (d, 2, J = 14 Hz), 4.57 (s, 1), and 9.62 (s, 1).

Anal. Calcd for $C_{14}H_{27}NO_3$: C, 65.33; H, 10.58. Found: C, 65.16; H, 10.55.

Heating **25** above its melting point (e.g., attempted purification by distillation) led to its conversion to **26**.

2,2-Dimethyl-3-[*N*-(4,4-dimethyl-1,3-oxazolidine)]propanal (26). A. Hemiacetal **25** (250 mg, 1 mmol) was stirred in methanol for 8 days at which time the methanol (and isobutyraldehyde) were removed in vacuo giving **26** as the only product detectable by GLC or ^1H NMR.

B. Hemiacetal **25** (500 mg, 2 mmol) was heated at reflux in dry dioxane for 4 h, then cooled, and the solvent removed in vacuo to give 320 mg (89%) yield of **26** as the only product.

For **26**: bp (pot) ca. 80 °C (0.5 mm); ir ($CHCl_3$) 2925, 2860, 2815, 2710, 1725, 1465, and 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (s, 6), 1.09 (s, 6), 2.64 (s, 2), 3.62 (s, 2), 4.38 (s, 2), 9.50 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 185 (5, M^+), 184 (6), 170 (20), 155 (30), 114 (56), 100 (54), 70 (47), and 42 (100).

Acknowledgment. We wish to thank the National Cancer Institute (CA 17115) for support of this work.

Registry No.—**4**, 58384-41-1; **7**, 58384-42-2; **8**, 58384-43-3; **9**, 40910-26-7; **10**, 40910-25-6; **11**, 40910-27-8; **13a**, 58384-44-4; **13b**, 58384-45-5; **13c**, 58384-46-6; **16**, 58384-47-7; **17**, 58384-48-8; **18**, 58384-49-9; **19**, 58384-50-2; **20**, 58384-51-3; **22**, 58384-52-4; **24**, 58384-53-5; **25**, 58384-54-6; **26**, 58384-55-7; 1-butanol, 71-36-3; 2-amino-2-methyl-1-propanol, 124-68-5; ethyl 2-bromoisobutyrate, 600-00-0; methyllithium, 917-54-4.

Supplementary Material Available. The ^{13}C NMR spectra of triols **22** and **24** (Figure 2) and the ^1H NMR spectrum of ϵ-hemiacetal **25** (Figure 3) (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) Presented in part at the 6th Northeast Regional Meeting of the American Chemical Society, Burlington, Vt., August 18, 1974; (b) P. Y. Johnson, I. Jacobs, and D. J. Kerkman, *J. Org. Chem.*, **40**, 2710 (1975); (c) P. Y. Johnson and I. Jacobs, *Synth. Commun.*, **4**, 51 (1974).

(2) P. Y. Johnson and I. Jacobs, *J. Chem. Soc., Chem. Commun.*, 925 (1972).

(3) (a) H. Möhrle and D. Schnädelbach, *Arch. Pharm. (Weinheim, Ger.)*, **308**, 352 (1975); (b) H. Möhrle and D. Schnädelbach, *ibid.*, **308**, 783 (1975).

(4) P. Y. Johnson and R. Silver, *J. Heterocycl. Chem.*, 1029 (1973).

(5) A preliminary report on some aspects of this work has appeared: P. Y. Johnson and M. Davis, *Tetrahedron Lett.*, 293 (1973).

(6) This molecule, which could be looked at as a potential 1,5-dialkylating agent in its diimmonium form, has been shown to display some activity against lymphocytic leukemia (P-388). Testing was performed by the National Cancer Institute.

(7) For dynamic ^1H NMR studies of related acyclic systems see ref 1b and references cited therein. Dynamic ^1H and ^{13}C NMR studies on lactone **9** have also been performed. A $\Delta G^{\ddagger}$ for nitrogen invession processes of 13.4 kcal/mol was found.

(8) For an early report on the acyloin reaction of an ester lactone containing molecule in the synthesis of colchicine see E. E. van Tamelen et al., *J. Am. Chem. Soc.*, **81**, 6341 (1959). For a discussion of this unusual type of acyloin reaction see J. J. Bloomfield, D. C. Owsley, and J. M. Nelke, *Org. React.*, **23**, 74 (1975).

(9) For a review of the reagent as an anion trapping agent see K. Rühlmann, *Synthesis*, 236 (1971).

(10) (a) The carbonyl band of *N-tert*-butyl-3,3,6,6-tetramethyl-1-azacycloheptan-4-on-5-ol[1b] also accurs at 1700 cm^{-1} when its infrared spectrum is taken under the same conditions. (b) Such a hydrogen bond would be expected to lower the carbonyl stretching frequency relative to the nonhydroxylated system given above.

(11) (a) E. E. van Tamelen et al., *Tetrahedron*, **14**, 8 (1961); (b) E. Fujita et al., *Tetrahedron Lett.*, 2573 (1969), and references cited therein.

(12) (a) P. v. R. Schleyer and L. Joris, *J. Am. Chem. Soc.*, **90**, 4599 (1968); (b) M. Oki et al., *Bull. Chem. Soc. Jpn.*, **41**, 176 (1968).

(13) M. Akhtar and S. Marsh, *J. Chem. Soc. C*, 937 (1966).

(14) For a review of chemical shift nonequivalence in prochiral groups see W. B. Jennings, *Chem. Rev.*, **75**, 307 (1975).

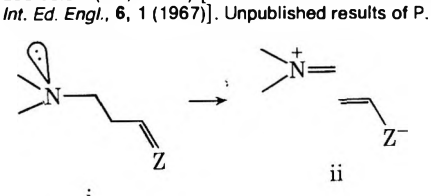
(15) While one would expect eight signals (four showing 6 H and four showing 3 H) attributable to the methyl protons in the ^1H NMR spectrum of **24** in the presence of a chiral shift reagent due to the formation of "pseudocontact" diastereomers,[15] this experiment was not run owing to lack of sample.

(16) See paragraph at end of paper regarding supplementary material.

(17) For examples of intramolecular capture of an OH group by an incipient immonium ion: (a) to give polycyclic systems see Y. Ban et al., *Tetrahedron Lett.*, 727 (1975); (b) to give a [3.3.1] bicyclic system see A. I. Meyers and C. C. Shaw, *ibid.*, 717 (1974).

(18) Mannich and reverse Mannich reactions involving 2,2-disubstituted ketones (but not aldehydes) have been the subject of considerable controversy. A discussion of the problem has been treated by G. L. Buchanan, A. C. Curran, and R. T. Wall, *Tetrahedron*, **25**, 5503 (1969), and references cited therein.

(19) Studies in our laboratories of the facile reverse Mannich reaction of hindered amino dialdehydes (e.g., **2** → **3**) indicate that stereoelectronic control in these systems seems to involve both (a) stereopopulation control [R. T. Borchardt and L. A. Cohen, *J. Am. Chem. Soc.*, **94**, 9166 (1972), and references cited therein] and (b) synchronous heterolytic fragmentation shown generalized below (i.e., i → ii) [C. A. Grob and P. W. Schiess, *Angew. Chem., Int. Ed. Engl.*, **6**, 1 (1967)]. Unpublished results of P. Y. Johnson.



i ii

(20) While we feel that ions **28** and **29** are intermediates in these reactions, direct five-membered ring formations (i.e., **28** → **26** and **29** → **31**) are unlikely since such processes would involve highly unfavorable endocyclic ring closures.

The Hofmann–Loeffler Hydrogen Abstraction Process in the Mass Spectrometry of 1-Alkoxy-9-methyl-9-azabicyclo[3.3.1]nonanes

Herman O. Krabbenhoft[1]

Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48104

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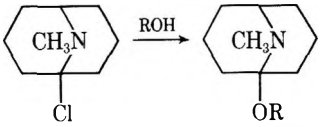
The electron impact induced fragmentation pathways of 15 bridgehead ethers in the 9-methyl-9-azabicyclo-[3.3.1]nonane system have been studied. The intensities of the base ions, as well as other fragment ions, are found to depend on the nature of the branching in the alkoxy group. The primary and secondary ethers display base peaks at *m/e* 112 which are formulated as arising by ejection of a lone pair electron from nitrogen, scission of the 1,2 bond, expulsion of cyclopropane, and loss of the alkyl portion of the alkoxy group. The latter two steps are supported by the observation of appropriate metastable peaks. The tertiary ethers have their base peaks at *m/e* 113 which are accounted for by invoking a hydrogen transfer from the alkoxy group to nitrogen, either by a McLafferty type rearrangement *subsequent* to α-cleavage or by a Hofmann–Loeffler type free radical abstraction *prior* to loss of the alkoxy group and α-cleavage. Evidence corroborating the latter process is presented. Other important primary ions occur at *m/e* values of 126, 138, 154, and 156; the mechanisms of their formations are described.

Based upon the definitive studies from the laboratories of Wawzonek[2a] and Corey[2b] the initial phases of the Hofmann–Loeffler reaction[3] are believed to involve homolysis of the nitrogen–halogen bond of an *N*-haloammonium ion to afford a nitrogen radical cation which abstracts a hydrogen intramolecularly from a δ carbon to generate a carbon radical. Since nitrogen cation radicals are produced in the electron impact induced ionization of amines, it might be expected that a Hofmann–Loeffler type hydrogen abstraction process should also take place in the mass spectrometer. In this report evidence implicating such an occurrence is presented.

Results and Discussion

The present mass spectrometric investigation was prompted by the observation that α-amino bridgehead ethers **1** and **14** exhibit different base peaks: ethyl ether **1** has its most abundant peak at *m/e* 112, whereas *tert*-amyl ether **14** displays its most intense peak at *m/e* 113. The constitutions of the *m/e* 112 and 113 ions were determined by high-resolution mass spectrometry to be $C_6H_{10}NO$ (found: 112.07714) and $C_6H_{11}NO$ (found: 113.08406). To probe the effect of the alkyl portion of the alkoxy group on the essence of the base peak, a number of α-amino bridgehead ethers were prepared by the alcoholysis of 1-chloro-9-methyl-9-azabicyclo[3.3.1]nonane[4] (eq 1). Table I presents the structures of the alkyl groups



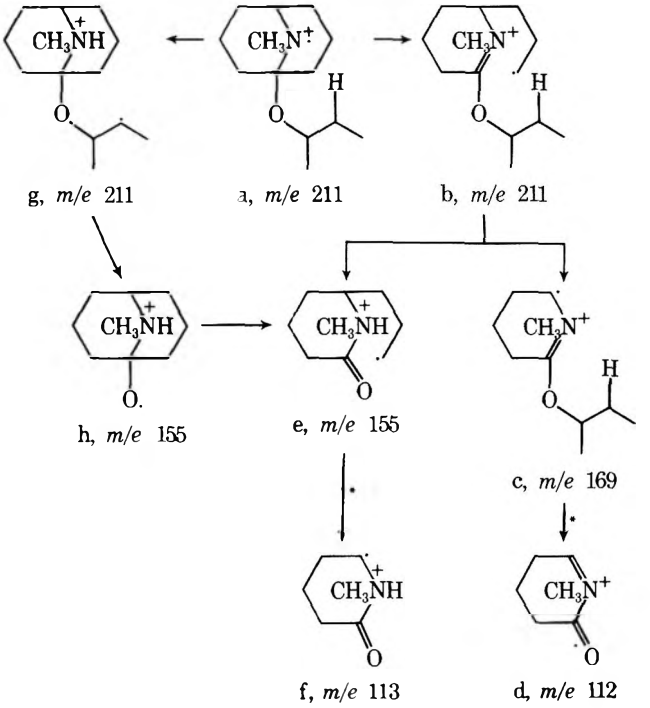
(1)

1, R = CH_2CH_3
14, R = $C(CH_3)_2CH_2CH_3$
17, R = C_6H_5

utilized in the present study along with pertinent relative intensity data.[5]

Upon inspection of the data in Table I it is seen that the most striking feature is the strong dependence of the relative abundances of a number of fragment ions, especially the base ions, upon the nature of the alkyl portion of the alkoxy group. For the *straight chain primary* ethers the base peaks are at *m/e* 112; the peaks at *m/e* 113 are actually quite small, since the isotopic P + 1 contributions from the *m/e* 112 ions are 7.1%. The *branched chain primary* ethers also show base peaks at *m/e* 112, but the intensities of the *m/e* 113 peaks are somewhat greater than those observed for the straight chain ethers. The *secondary* ethers display base peaks at *m/e* 112; however, the abundances of the *m/e* 113 peaks are substantial. Finally, the *tertiary* ethers have their base peaks at *m/e* 113,

Chart I



although the *m/e* 112 peaks are still rather intense. The mass spectra[6] of the butyl ethers are typical of the various classifications of ethers, and illustrate the trends of branching outlined above. Clearly, both the degree and position of branching are important in determining the relative intensities of the base peaks.

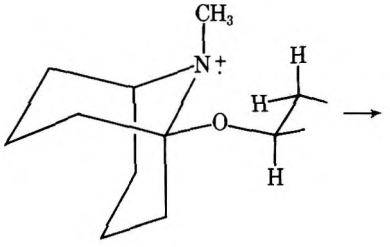
Chart I contains the proposed fragmentation pathways leading to the production of the base peaks; 2-butyl ether **10** is employed as the model substrate. Based on ionization potentials[7] and other studies[8,9] it can be assumed that upon electron bombardment, an electron is preferentially ejected from the lone pair of electrons on nitrogen rather than from a lone pair on oxygen; the fragmentation sequences are triggered by radical cation a. A primary decomposition process is the usual homolytic cleavage of a carbon–carbon bond adjacent to nitrogen to provide the immonium ion b. Such a bond rupture is typical of amines[10] and is well documented by the mass spectra of derivatives of the alkaloids tropane[11] and granatanine.[12] Scission of the 1,2 bond is expected to be preferable to 4,5-bond cleavage, since in the former instance the ether oxygen atom can also stabilize the intermediate cationic species. Radical ion b is transformed into radical

Table I. Relative Intensity Data for α-Amino Bridgehead Ethers

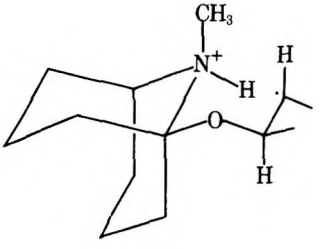
Compd	Alkyl group	M^+	M − 29	M − 42	*m/e* 110	*m/e* 112	*m/e* 113	*m/e* 126	*m/e* 138	*m/e* 154	*m/e* 155	*m/e* 156
1	CH_3CH_2	33	52	15	8	100	7	19	5	52	6	1
2	$CH_3CH_2CH_2$	16	11	8	6	100	8	17	4	23	8	1
3	$CH_3(CH_2)_2CH_2$	11	11	4	4	100	9	17	4	20	3	3
4	$CH_3(CH_2)_3CH_2$	10	8	4	6	100	9	16	4	20	3	4
5	$(CH_3)_2CHCH_2$	8	5	4	9	100	15	27	7	20	4	20
6	$C_2H_5(CH_3)CHCH_2$	12	8	4	7	100	22	34	10	26	6	49
7	$(CH_3)_2CHCH_2CH_2$	14	9	4	8	100	15	23	8	26	6	37
8	$(CH_3)_3CCH_2$	40	9	21	20	100	63	70	28	45	20	18
9	$(CH_3)_2CH$	21	4	9	15	100	33	44	7	31	9	1
10	$CH_3CH_2(CH_3)CH$	13	2	2	16	100	49	53	15	26	8	20
11	n-$C_3H_7(CH_3)CH$	22	3	2	14	100	59	55	18	34	12	45
12	$(CH_3CH_2)_2CH$	18	2	2	26	100	78	69	36	32	15	50
13	$(CH_3)_3C$	14	1	1	17	76	100	69	14	5	42	5
14	$CH_3CH_2(CH_3)_2C$	4	1	1	27	46	100	71	33	4	45	7

cation c ($M^+ - 42$) by the expulsion of cyclopropane; a metastable peak corresponding to the b → c transition was observed for some of the substrates.[13] Subsequent loss of the alkyl portion of the alkoxy group of c results in the formation of the *m/e* 112 ion (d). The c → d step is also supported by appropriate metastable peaks for several of the compounds.

There are two similar mechanisms by which the radical ion at *m/e* 113 can be generated. In one pathway a hydrogen from the alkoxy side chain is transferred to nitrogen with concomitant expulsion of the alkyl portion to produce e (*m/e* 155) from b. Such a migration–elimination process is closely related mechanistically to the McLafferty rearrangement.[14] Expulsion of cyclopropane from e (substantiated by metastable peaks in numerous instances) gives the *m/e* 113 ion (f). The alternate sequence leading to the production of the *m/e* 113 peak consists of hydrogen abstraction from the alkoxy side chain by the initially generated nitrogen radical cation a to provide the isomeric ammonium radical g. Subsequent loss of an alkene affords the ammonium alkoxy radical (*m/e* 155) which undergoes scission of the 1,2 bond to give the isomeric species e which goes on to f (*m/e* 113) as indicated above. The a → g process is ideally suited conformationally (eq 2) to compete effectively with the usual α-cleavage mechanism and is completely analogous to the hydrogen abstraction portion of the condensed phase Hofmann–Loeffler reaction.



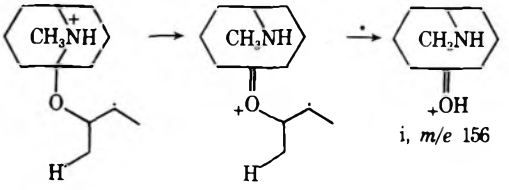
a



g (2)

One line of evidence which is supportive of the Hofmann–Loeffler type process is the general increase in the relative intensities of the *m/e* 156 ion as one proceeds from primary to secondary (but not tertiary) ethers; the intensities of the *m/e* 156 ions tend to parallel those of the *m/e* 113 ions. Since the 1-oxy-9-methyl-9-azabicyclo[3.3.1]nonane framework has

Chart II



g, *m/e* 211 g′, *m/e* 211 i, *m/e* 156

a molecular weight of 154, two hydrogens must be added to the nucleus to obtain a species of *m/e* 156. With the McLafferty rearrangement (b → e) a hydrogen can be transferred to nitrogen only with the simultaneous elimination of the side chain. Thus, the McLafferty rearrangement generates an ion of *m/e* 155, but provides no viable means of adding the second hydrogen. The Hofmann–Loeffler process, on the other hand, does not require the expulsion of the side chain. The radical cation g can transfer a hydrogen to oxygen with concomitant ejection of the side chain as a stable allylic radical to form the *m/e* 156 ion i (Chart II). This latter process is substantiated by the detection of appropriate metastable peaks on several occasions.[15] The only apparent exceptions to the trend relating the intensities of the *m/e* 113 and 156 ions are isopropyl ether 9 and tertiary ethers 13 and 14 which show relatively small magnitudes for the *m/e* 156 ions even though the *m/e* 113 ions are of substantial abundance. However, such results would be predicted for these substrates. Hydrogen abstraction by nitrogen (a → g) generates a primary carbon radical in these cases. To circumvent the intermediacy of a primary radical, the elimination of the side chain occurs in concert with the Hofmann–Loeffler hydrogen migration to nitrogen, and essentially precludes the production of the *m/e* 156 ion (h).

Further evidence militating against the McLafferty rearrangement comes from the mass spectrum of neopentyl ether 8. It has been determined that the McLafferty rearrangement proceeds mainly through a six-membered transition state[14] which is not possible with 8. The Hofmann–Loeffler free radical abstraction mechanism has been found not to be confined to this restriction.[4] For neopentyl ether 8 a seven-membered transition state serves to transfer a hydrogen to nitrogen, while migration of a second hydrogen to oxygen is accompanied by the elimination of a cyclopropylcarbinyl radical to produce h.

The fact that the relative intensities of the *m/e* 113 ions increase as the number of hydrogens suitable for transference to nitrogen via a six-membered transition state increases (from one or two for the primary ethers to five or six for the secondary ethers to eight or nine for the tertiary ethers) is also in complete accord with the involvement of the Hofmann–Loeffler type hydrogen abstraction process. For the secondary

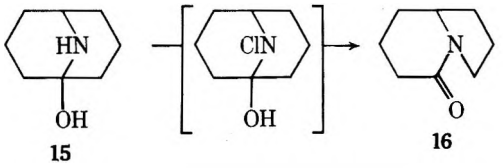
and tertiary ethers the hydrogens capable of participating in a six-membered transition state are mostly primary, but just as in the Hofmann–Loeffler reaction the proximity of the hydrogen to nitrogen is usually more important than its substituent nature. A similar situation exists for the mechanistically related Barton reaction[16] which has also been found to occur in the mass spectrometer.[17] The branched chain primary ethers have their *m/e* 113 ions more intense than the straight chain primary ethers probably owing to the availability of tertiary hydrogens in the former substrates.[3]

In summary, based upon the observations and arguments made above, the Hofmann–Loeffler type hydrogen abstraction process is a perfectly viable mode of fragmentation in the mass spectrometer, and at least for some of the substrates studied here can compete effectively with the usual α-cleavage mechanism.

Besides the *m/e* 112 and 113 ions and their progenitors, the peaks at *m/e* 154, 138, 126, and 110 are of significant intensity. Chart III presents the proposed fragmentations leading to the ions at *m/e* 138 and 110. Loss of alkoxyl from molecular ion a produces immonium ion j (*m/e* 138)[18] which undergoes a retrograde Diels–Alder reaction to give k (*m/e* 110).

The *m/e* 126 ion is accounted for as shown in Chart IV. Intramolecular abstraction of the bridgehead hydrogen within b produces l which loses ethyl radical to afford m ($M^+ - 29$) which goes on to the *m/e* 126 ion n by way of a McLafferty type rearrangement. The last step of the proposed sequence is supported by the detection of metastable peaks on many occasions.

The *m/e* 154 ion formation is rationalized by the (perhaps concerted) loss of the alkyl side chain and migration of the 2 carbon atom to the nitrogen radical a to provide the quaternary amide cation o (Chart V).[19] In support of the Wagner–Meerwein type fragmentation advocated in Chart V is the finding that treatment of amino alcohol **15** with calcium hypochlorite gave a nearly quantitative yield of lactam **16** (eq 3).[20]



15 **16** (3)

Finally, the mass spectrum of phenyl ether **17**[6,21] clearly demonstrates the importance of the side chain on the fragmentation pathways of the α-amino bridgehead ethers (Chart VI). Most of the primary fragmentation processes (Charts I, II, IV, V) observed for the *alkyl* ethers are substantially retarded. Since phenyl radical is a much poorer leaving group than an alkyl radical, production of the *m/e* 112 ion is reduced from 100% relative intensity for the alkyl ethers to 13% for aromatic ether **17**. The phenyl group also precludes the migration of a hydrogen to nitrogen, since only aryl hydrogens are available, and thus the terminal ions f (*m/e* 113), h (*m/e* 156), and m (*m/e* 126) as well as intermediate ion e (*m/e* 155) are not observed in the mass spectrum of **17**.

Chart III

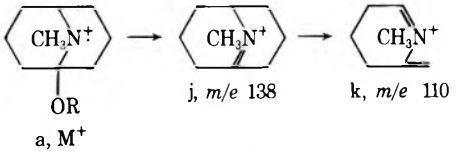


Chart IV

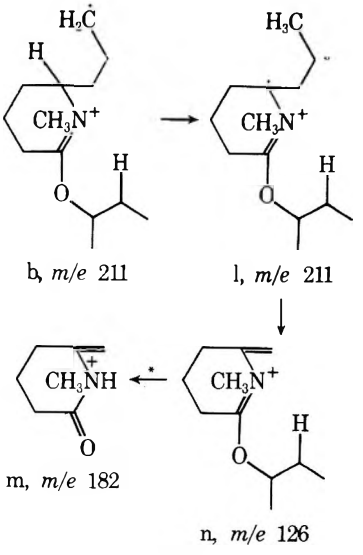


Chart V

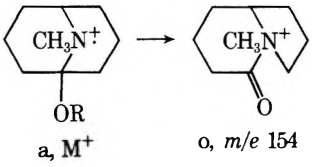
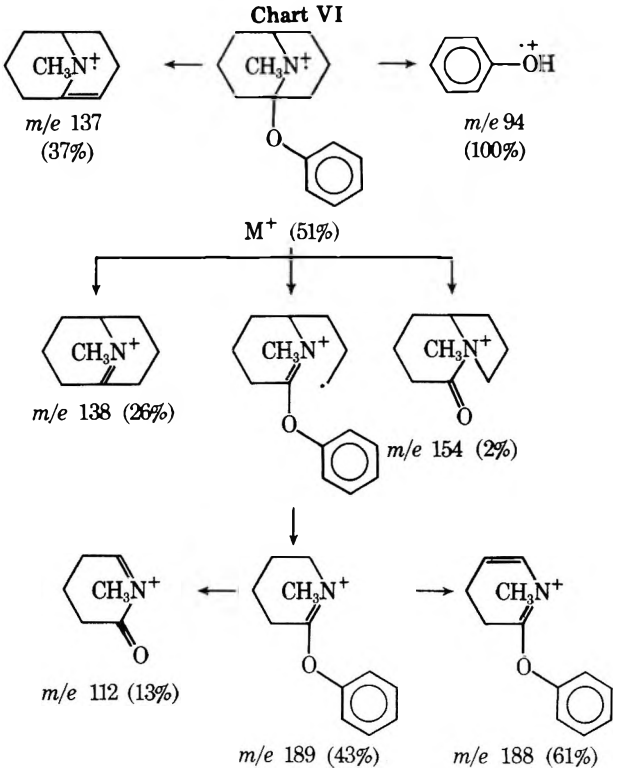


Chart VI



Experimental Section

Mass spectra were obtained with an A. E. I. MS-9 mass spectrometer at 70 eV; source temperatures were about 160 °C.

1-Alkoxy-9-methyl-9-azabicyclo[3.3.1]nonanes (1–14). Approximately 300 mg of 1-chloro-9-methyl-9-azabicyclo[3.3.1]nonane[4] was dissolved in 30 ml of the appropriate alcohol. To these solutions were added 100 mg of NaOH and 500 mg of $AgNO_3$, and the resulting mixtures stirred in the dark at room temperature for 2 h, after which the reactions were processed by filtration, addition of CH_2Cl_2 and H_2O to the filtrates, separation of the phases, washing of the organic layers with H_2O and saturated aqueous NaCl solution, drying over Na_2SO_4, and concentration with a rotary evaporator. Crude yields of products were in the 50–85% range. Pure samples of **1–14** (all of which are oils) for spectra[22] and elemental analyses[23] were obtained by preparative GC with a Varian Aerograph Model 90-P gas chromatograph utilizing a 6 ft × 0.25 in. stainless steel column containing 5% SE-30 on Chromosorb G; the column temperatures employed for sample collection

were about 190 °C (which established that the substrates are thermally stable for the conditions used on the mass spectrometer).

1-Phenoxy-9-methyl-9-azabicyclo[3.3.1]nonane (17). To a solution of 1-chloro-9-methyl-9-azabicyclo[3.3.1]nonane in 5 ml of benzene were added 1.0 g of phenol and 0.200 g of $AgNO_3$. After stirring in the dark at room temperature for a couple of hours the reaction mixture was worked up by adding H_2O and CH_2Cl_2, separating layers, washing the organic phase with 5% aqueous NaOH solution, H_2O, and saturated aqueous NaCl solution, drying over K_2CO_3, and concentrating under vacuum. Pure **17** was obtained from preparative GC as an oil: NMR ($CDCl_3$) δ 6.7–7.5 (m, 5 H), 3.13 (br m, 1 H), 2.52 (s, 3 H), 0.9–2.5 (12 H).

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.85; H, 9.20; N, 6.06.

1-Azabicyclo[4.3.0]nonan-2-one (16). Utilizing the procedure of Gassman and Cryberg[24] a solution prepared from 693 mg (4.91 mmol) of **15**[4] and a minimum volume of H_2O was basicified with 5% aqueous NaOH solution, treated with 2 g of $Ca(OCl)_2$ and 10 ml of H_2O, and stirred at room temperature for 0.5 h, after which the reaction mixture was worked up by extraction with CH_2Cl_2, washing the combined extracts with water and saturated aqueous NaCl solution, drying over Na_2SO_4, and concentrating under vacuum to give 647 mg (93%) of an oil which was shown by GC analysis to consist of only one component and whose ir and NMR spectra were identical with those reported previously for **16**.[25]

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Registry No. — **1**, 58408-47-2; **2**, 58408-48-3; **3**, 58408-49-4; **4**, 58408-50-7; **5**, 58408-51-8; **6**, 58408-52-9; **7**, 58408-53-0; **8**, 58408-54-1; **9**, 58408-55-2; **10**, 58408-56-3; **11**, 58408-57-4; **12**, 58408-58-5; **13**, 58408-59-6; **14**, 58408-60-9; **17**, 58408-61-0; 1-chloro-9-methyl-9-azabicyclo[3.3.1]nonane, 51209-45-1; phenol, 108-95-2; ethanol, 64-17-5; 1-propanol, 71-23-8; 1-butanol, 71-36-3; 2-methyl-1-propanol, 78-83-1; 2-methyl-1-butanol, 137-32-6; 3-methyl-1-butanol, 123-51-3; 2,2-dimethyl-1-propanol, 75-84-3; 2-propanol, 67-63-0; 2-butanol, 78-92-2; 2-pentanol, 6032-29-7; 3-pentanol, 584-02-1; 2-methyl-2-propanol, 75-65-0; 2-methyl-2-butanol, 75-85-4.

Supplementary Material Available. Bar graphs of the spectra of the butyl ethers (**3**, **5**, **10**, and **13**) and phenyl ether **17** and tables of metastable peaks and ^1H NMR spectral data for compounds **1–14** (8 pages). Ordering information is given on any current masthead page.

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A B

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Selective Reductions. XXI. 9-Borabicyclo[3.3.1]nonane in Tetrahydrofuran as a New Selective Reducing Agent in Organic Synthesis. Reaction with Selected Organic Compounds Containing Representative Functional Groups[1]

Herbert C. Brown,* S. Krishnamurthy,[2a] and Nung Min Yoon[2b]

Richard B. Wetherill Laboratory, Purdue University, West Lafayette, Indiana 47907

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The approximate rates, stoichiometry, and products of the reaction of 9-borabicyclo[3.3.1]nonane (9-BBN) with selected organic compounds containing representative functional groups under standard conditions (tetrahydrofuran, 25 °C) were determined in order to establish the utility of the reagent as a selective reducing agent. Primary, secondary, and tertiary alcohols and simple phenols evolve hydrogen rapidly and quantitatively. However, 2,6-di-*tert*-butylphenol is inert to this reagent even at 65 °C. Reaction with *n*-hexylamine and thiols is quite sluggish. Aldehydes and ketones of diverse structure are reduced rapidly and quantitatively to give the corresponding alcohols in excellent yields. However, the highly hindered ketone 2,2,4,4-tetramethyl-3-pentanone is quite inert even at 65 °C. Reduction of 2-methylcyclohexanone gives 40% *cis*- and 60% *trans*-2-methylcyclohexanol, respectively. Cinnamaldehyde is rapidly and cleanly reduced to cinnamyl alcohol; it undergoes further hydroboration very slowly. Anthraquinone is cleanly reduced to 9,10-dihydro-9,10-anthracenediol in 79% yield. Carboxylic acids liberate hydrogen rapidly and quantitatively and further reduction is very slow. However, in refluxing THF *n*-octanoic acid is reduced to *n*-octyl alcohol quantitatively in 24 h. Acid chlorides are reduced rapidly and quantitatively to the corresponding alcohols. Esters are reduced at a moderate rate at room temperature. However, at 65 °C complete reduction can be achieved in 4 h. γ-Butyrolactone is reduced to 1,4-butanediol at a moderate rate whereas the reduction of phthalide is very slow. Both *n*-octyl bromide and *p*-bromotoluene are inert toward his reagent. Epoxides such as 1,2-butylene oxide react very sluggishly. However, the presence of a catalytic quantity of borohydride enhances the rate dramatically. Primary amides evolve one hydrogen and further reaction is very slow. Tertiary amides are rapidly reduced to give alcohols as the major product. Nitriles are reduced slowly. 1-Nitropropane is inert, whereas nitrobenzene reacts very slowly. Azobenzene is inert whereas azoxybenzene is slowly reduced to the azobenzene stage. Cyclohexanone oxime liberates hydrogen rapidly and undergoes slow reduction to *N*-cyclohexylhydroxylamine. Phenyl isocyanate is rapidly reduced to the imine stage and further reduction is very slow. Pyridine and pyridine *N*-oxide undergo slow reduction. Dimethyl sulfoxide is reduced at a moderate rate, whereas the other sulfur compounds tested—disulfides, sulfide, sulfone tosylate, and sulfonic acids—are inert to this reagent under standard conditions. Kinetics of the reaction of 9-BBN with various readily reacting functional groups indicate that the dissociation of dimeric 9-BBN is the rate-determining step in these reactions. Relative reactivity studies on functional groups by competition experiments reveal that cyclohexanone can be reduced without significant attack on cyclopentene, cyclopentene can be hydroborated with total exclusion of ester, and acid chlorides can be reduced quantitatively without significant attack on esters.

The discovery of the hydroboration reaction in 1956 has made available a number of partially alkylated borane derivatives.[3] Among them 9-borabicyclo[3.3.1]nonane (9-BBN), a bicyclic dialkylborane obtained by the cyclic hydroboration of 1,5-cyclooctadiene, exhibits certain remarkable physical and chemical characteristics quite distinct from those of borane and other mono- and dialkylboranes.[4] It is a white, crystalline solid (mp 154–155 °C), exceptionally stable thermally, relatively insensitive to air, and soluble in a variety of organic solvents. It hydroborates olefins with exceptionally high regio- and stereoselectivity, far greater than those observed with borane and other dialkylboranes.[5] *B*-alkyl and *B*-aryl derivatives of 9-BBN have proved highly effective in the stereoselective synthesis of carbon structures through the selective migration of the alkyl or aryl group on boron.[3]

We recently reported an extensive investigation of the approximate rates and stoichiometry of the reaction in tetrahydrofuran (THF) at 0 °C of borane, thexylborane, and disiamylborane with organic compounds containing representative functional groups.[6] The remarkable properties of 9-BBN discussed earlier together with its commercial availability[7] persuaded us of the desirability of making a related systematic study of the reducing characteristics of this new reagent.

Accordingly, we undertook a detailed examination of the rate, stoichiometry, and products of the reaction of 9-BBN with representative functional groups and its applicability for selective reductions in organic synthesis. The results of these investigations are reported in the present paper.

Results and Discussion

Standard Solution of 9-BBN. Solutions of 9-BBN in tetrahydrofuran were prepared either by the stoichiometric hydroboration of 1,5-cyclooctadiene with borane–THF at 0 °C and refluxing the resulting mixture for 2 h or by dissolving a calculated amount of commercial 9-BBN powder in dry THF to give the desired concentration. The concentration was determined by hydrolyzing a known aliquot of the solution with methanol–THF (1:1) at 25 °C and measuring the hydrogen evolved.

Such solutions are stable indefinitely under dry nitrogen atmosphere.

Procedure for Rate and Stoichiometry Studies. In order to define the reduction characteristics of 9-BBN, we undertook to examine the reaction of 70 organic compounds containing representative functional groups with excess 9-BBN. The procedure adopted was to add 5 mmol of the organic compound containing a representative functional group to 20 mmol of 9-BBN in sufficient tetrahydrofuran to give 40 ml solution. This made the reaction mixture 0.5 M in 9-BBN and 0.125 M in the compound under examination.[8] The solutions were maintained at constant temperature (ca. 25 °C) and the aliquots were removed at appropriate intervals of time and analyzed for "residual hydride" by hydrolysis.[9]

In this manner it was possible both to establish the rate at which reduction proceeds and the stoichiometry of the reaction, i.e., the number of hydrides utilized per mole of compound when the reaction comes to an effective halt.

Product Analysis by GLC. Having established the approximate rate and stoichiometry of the reaction, it was desirable to establish the nature of the products (and the intermediates in some typical cases) wherever it is interesting and offers possibility for selective reduction. Further, even with functional groups which are inert it was of interest to examine whether the compound can be recovered without any loss after prolonged contact with 9-BBN.

Accordingly, separate reactions on a 5-mmol scale were carried out. Either essentially a stoichiometric amount of 9-BBN or excess was utilized depending upon the functional group. In some instances, the temperature was raised to refluxing THF to shorten the reaction time.

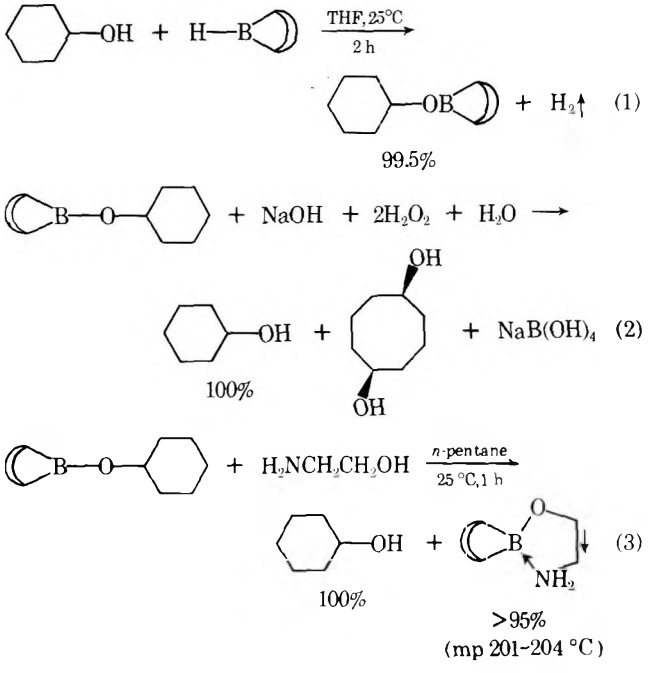
The products were identified by GLC comparison with authentic samples. Yields were determined, also by GLC analysis, utilizing internal standards and standard synthetic mixtures.

Procedures for the Isolation of the Reaction Products. Removal of 9-BBN Moiety from the Reaction Mixture. A large number of organic functional groups, such as alcohol, aldehyde, ketone, carboxylic acid, ester, acid chloride, amide, epoxide, etc., after reduction with 9-BBN end up as the *B*-alkoxy-9-BBN derivative. Consequently, a convenient separation of the alcohol from the 9-BBN moiety is highly desirable. We prepared *B*-cyclohexyloxy-9-BBN and explored various procedures for the recovery of cyclohexanol from 9-BBN moiety (eq 1).

Initially, we explored the feasibility of simply extracting from the organic phase *B*-hydroxy-9-BBN, produced on hydrolysis, with various complexing agents, such as sodium hydroxide, mannitol, etc. Various proportions of solvent mixtures were also examined (pentane–THF). However, these procedures were not satisfactory.

Finally, further research in this direction led to the development of two convenient workup procedures. The reaction mixture can be treated with alkaline hydrogen peroxide[10] to oxidize the 9-BBN moiety and the product separated by distillation from the *cis*-1,5-cyclooctanediol (procedure A) (eq 2).

Alternatively and more conveniently, the THF can be removed under vacuum from the reaction mixture and pentane added. The addition of 1 mol of ethanolamine precipitates the 9-BBN as the adduct. Removal of the pentane solution followed by distillation yields the product (procedure B)[11] (eq 3).

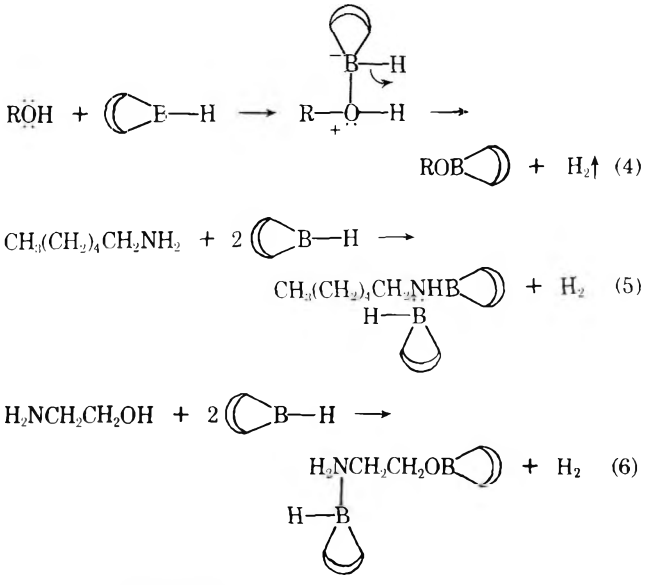


In addition to pentane, ether and benzene also work quite satisfactorily, as revealed by the recovery of cyclohexanol in yields of 100 and 97%, respectively. In a typical experiment utilizing ether as the solvent, the 9-BBN adduct of ethanolamine was isolated in 94% yield. Unfortunately, this adduct is soluble in THF.[12]

This serves as an excellent neutral workup procedure for compounds containing acid- and base-sensitive groups. Utilizing this procedure, a variety of products were isolated in 78–86% yield.

Rate and Stoichiometry. Alcohols, Phenols, Amines, and Thiols. All of the simple alcohols examined (primary, secondary, and tertiary) liberate hydrogen rapidly and quantitatively. While the primary and secondary alcohols require only 10 min for complete hydrogen evolution, tertiary alcohol requires 30 min. However, the highly hindered alcohol 2,2,4,4-tetramethyl-3-pentanol requires 6 h for complete hydrogen evolution under standard conditions. The product in all of these cases is the *B*-alkoxy-9-BBN. Thus, stoichiometric reaction of 9-BBN with 1-hexanol liberates hydrogen quantitatively in 60 min to give 100% yield of *B*-*n*-hexyloxy-9-BBN as determined by NMR using benzene as internal standard. The alcohol can be regenerated quantitatively either by simple hydrolysis or by treating with 2-aminoethanol in *n*-pentane. Phenol, 2,6-dimethylphenol, and 2,6-diisopropylphenol evolve hydrogen quantitatively in 30 min. However, 2,6-di-*tert*-butylphenol is completely inert toward 9-BBN; even under reflux (65 °C) no hydrogen evolution is observed in 24 h. This could be attributed to the inability of 9-BBN to coordinate with the oxygen atom of this phenol, presumably the first step in the protonolysis reaction (eq 4).

Both *n*-hexanethiol and benzenethiol are sluggish in their reactions. *n*-Hexylamine evolves only 1 equiv of hydrogen at 65 °C. However, hydrolysis of the reaction mixture with methanol–THF protonolyzes only 2 of the 3 equiv of 9-BBN remaining. The addition of 6 N HCl protonolyzes the third equivalent. Presumably we are forming an amine–borane complex (eq 5). Similarly, 9-BBN evolves hydrogen rapidly with 2-aminoethanol. Here again the hydrolysis of the third equivalent of 9-BBN requires 6 N HCl, indicating the formation of amine–borane complex (eq 6).



The results are summarized in Table I.

Aldehydes and Ketones. Simple aldehydes and ketones, both alkyl and aryl, consume 1 equiv of hydride, indicating clean reduction to the corresponding *B*-alkoxy-9-BBN (eq 7). Indeed, stoichiometric reduction of *n*-hexanal with 9-BBN gives a quantitative yield of *B*-*n*-hexyloxy-9-BBN (deter-

Table I. Reaction of 9-Borabicyclo[3.3.1]nonane with Representative Alcohols, Phenols, Amines, and Thiols in Tetrahydrofuran at 25 °C[a]

Registry no.	Compd	Time, min	Hydrogen evolved[b]	Hydride used[b]	Hydride used for redn[b]
67-56-1	Methanol	1	0.68	0.68	0.00
		2	0.88	0.88	0.00
		5	0.98	0.98	0.00
		10	1.00	1.00	0.00
111-27-3	1-Hexanol	5	0.95	0.95	0.00
		10	1.00	1.00	0.00
		30	1.00	1.00	0.00
100-51-6	Benzyl alcohol	30	1.03	1.03	0.00
		60	1.03	1.03	0.00
623-37-0	3-Hexanol	2	0.93	0.93	0.00
		5	0.97	0.97	0.00
		10	1.00	1.00	0.00
		30	1.00	1.00	0.00
597-49-9	3-Ethyl-3-pentanol	5	0.61	0.61	0.00
		10	0.77	0.77	0.00
		15	0.89	0.89	0.00
		30	1.00	1.00	0.00
		60	1.00	1.00	0.00
14609-79-1	2,2,4,4-Tetramethyl-3-pentanol	15	0.20	0.20	0.00
		30	0.29	0.29	0.00
		180	0.76	0.76	0.00
		360	1.00	1.00	0.00
108-95-2	Phenol	5	0.64	0.64	0.00
		10	0.79	0.79	0.00
		15	0.88	0.88	0.00
		30	1.00	1.00	0.00
576-26-1	2,6-Dimethylphenol	2	0.48	0.48	0.00
		5	0.70	0.70	0.00
		10	0.96	0.96	0.00
		15	0.99	0.99	0.00
		30	1.05	1.06	0.01
2078-54-8	2,6-Diisopropylphenol	2	0.50	0.50	0.00
		5	0.74	0.74	0.00
		10	0.98	0.98	0.00
		15	1.03	1.03	0.00
		360	1.03	1.03	0.00
128-39-2	2,6-Di-*tert*-butylphenol	60	0.00	0.00	0.00
		720	0.00	0.00	0.00
		1440	0.02	0.02	0.00
		60[c]	0.00	0.00	0.00
		360[c]	0.00	0.00	0.00
		1440[c]	0.00	0.00	0.00
111-31-9	1-Hexanethiol	60	0.40	0.40	0.00
		180	0.81	0.81	0.00
		360	0.99	0.99	0.00
		1440	1.00	1.00	0.00
108-98-5	Benzenethiol	180	0.68	0.68	0.00
		360	0.84	0.84	0.00
		720	0.95	0.95	0.00
		1440	1.00	1.00	0.00
111-26-2	*n*-Hexylamine[d]	180	0.09	0.09	0.00
		900	0.11	0.11	0.00
		1440[c]	1.00	1.00	0.00
141-43-5	2-Aminoethanol[d]	2	0.96	0.96	0.00
		5	1.04	1.04	0.00
		10	1.04	1.04	0.00

[a] 5.0 mmol of compound was added to 20 mmol of 9-BBN (20 mmol of hydride in 40 ml of solution; 0.125 M in compound and 0.5 M in hydride). [b] mmol/mmol of compound. [c] Refluxing tetrahydrofuran. [d] Hydrolysis with 6 N hydrochloric acid.

mined by NMR using benzene as the internal standard), identical with the product obtained by the reaction of 9-BBN with 1-hexanol.

$$R_2CO + H\text{—}B\langle \xrightarrow[25°]{THF} R_2CHOB\langle \qquad (7)$$

R = H, alkyl, aryl 95–100%

Cyclic and bicyclic ketones, such as cyclohexanone, 2-methylcyclohexanone, 4-*tert*-butylcyclohexanone, and norcamphor, are reduced completely in 30–60 min.

Hindered ketones, such as diisopropyl ketone and camphor, required 6 h for complete reduction. Highly hindered ketones, such as 2,2,4,4-tetramethyl-3-pentanone, proved inert toward 9-BBN. Even in refluxing THF, this ketone failed to react and was recovered in 96% yield after 24 h.

Cinnamaldehyde utilizes one hydride rapidly (<30 min) and the uptake of the second hydride is very slow and incomplete. An experiment carried out using a stoichiometric amount of

Table II. Reaction of 9-Borabicyclo[3.3.1]nonane with Representative Aldehydes and Ketones in Tetrahydrofuran at 25 °C[a]

Registry no.	Compd	Time, h	Hydrogen evolved[b]	Hydride used[b]	Hydride used for redn[b]
66-25-1	*n*-Hexanal	0.5	0.05	1.02	0.97
		1.0	0.05	1.05	1.00
100-52-7	Benzaldehyde	0.5	0.01	0.96	0.95
		1.0	0.01	1.01	1.00
110-43-0	2-Heptanone	0.5	0.07	1.08	1.01
		1.0	0.07	1.08	1.01
98-86-2	Acetophenone	0.5	0.06	1.03	0.97
		1.0	0.06	1.05	0.99
		3.0	0.06	1.05	0.99
119-61-9	Benzophenone	0.5	0.00	0.65	0.65
		1.0	0.00	0.93	0.93
		3.0	0.00	0.98	0.98
		12.0	0.00	0.98	0.98
565-80-0	Diisopropyl ketone	0.5	0.05	0.41	0.36
		1.0	0.05	0.62	0.57
		6.0	0.05	1.06	1.01
815-24-7	2,2,4,4-Tetrameth-yl-3-pentanone	1.0	0.00	0.00	0.00
		12.0	0.00	0.00	0.00
		24.0	0.00	0.00	0.00
		24.0[c]	0.00	0.00	0.00
108-94-1	Cyclohexanone	0.5	0.00	1.00	1.00
583-60-8	2-Methylcyclohexa-none	0.25	0.00	1.00	1.00
		1.0	0.00	1.00	1.00
1728-46-7	4-*tert*-Butylcyclo-hexanone	0.25	0.00	1.00	1.00
		1.00	0.00	1.00	1.00
497-38-1	Norcamphor	0.5	0.05	0.93	0.88
		1.0	0.05	0.98	0.93
		3.0	0.05	0.99	0.94
76-22-2	Camphor	0.5	0.00	0.67	0.67
		1.0	0.00	0.82	0.82
		3.0	0.00	0.94	0.94
		6.0	0.00	1.01	1.01
104-55-2	Cinnamaldehyde	0.5	0.02	0.98	0.96
		1.0	0.02	1.00	0.98
		3.0	0.02	1.05	1.03
		24.0	0.02	1.32	1.30
		48.0	0.02	1.52	1.50

[a–c] See the corresponding footnotes in Table I.

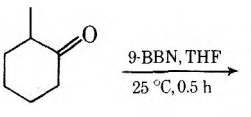
Table III. Stereochemistry of the Reduction of Representative Cyclic and Bicyclic Ketones with 9-Borabicyclo[3.3.1]nonane in Tetrahydrofuran at 25 °C

Registry no.	Ketone	Total yield, %	Less stable isomer	Percentage
591-24-2	2-Methylcyclohexanone	100	Cis	40
	3-Methylcyclohexanone	98	Trans	12
	4-*tert*-Butylcyclohexanone	99	Cis	8
	Norcamphor	100	Endo	91
	Camphor	100	Exo	75

9-BBN (1 equiv) gave a quantitative yield of cinnamyl alcohol. Consequently, we are achieving the rapid reduction of the aldehyde group followed by the very sluggish hydroboration of the double bond. The results are summarized in Table II.

Stereochemistry of the Reduction of Cyclic and Bicyclic Ketones with 9-BBN. A detailed study of the reaction of various dialkylboranes with representative monocyclic, bicyclic, and polycyclic ketones[13] revealed that dialkylboranes, such as disiamylborane and di-3-pinanylborane, exhibit remarkable consistency in directing the reduction of both α-substituted cycloalkanones and bicyclic ketones from the less hindered side to yield predominantly the less stable of the two possible epimers. Unfortunately, 9-BBN was not known when this study was carried out in our laboratory. Consequently, it was of interest to examine the ability of 9-BBN to introduce steric control into the reduction of such systems. Reactions were carried out at 25 °C utilizing essentially a stoichiometric quantity of 9-BBN (3–5% excess). The results are summarized in Table III.

2-Methylcyclohexanone gives only 40% cis isomer, significantly less than that observed with other dialkylboranes previously examined (eq 8). With 3-methyl- and 4-*tert*-



100% (40% cis) (8)

butylcyclohexanones, 9-BBN exerts little influence on the direction taken by the reduction. The product is predominantly the more stable of the two possible isomers. Reduction of bicyclic ketones, such as norcamphor and camphor, proceeds with preferential attack of the 9-BBN from the less hindered side, yielding the less stable of the two possible isomers predominantly (91% *endo*-2-norbornanol and 75% iso-

Table IV. Reaction of 9-Borabicyclo[3.3.1]nonane with Representative Quinones in Tetrahydrofuran at 25 °C[a]

Registry no.	Compd	Time, h	Hydrogen evolved[b]	Hydride used[b]	Hydride used for redn[b]
106-51-4	*p*-Benzoquinone[c]	1.0	0.37	0.40	0.03
		6.0	0.39	0.46	0.07
84-65-1	Anthraquinone[d]	0.5	0.00	0.72	0.72
		1.0	0.00	1.55	1.55
		3.0[e]	0.00	2.00	2.00

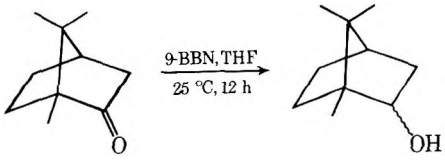
[a,b] See the corresponding footnotes in Table I. [c] White, gelatinous precipitate. [d] Reverse addition. After 2 h no solid anthraquinone was observed. [e] After methanolysis the resulting solution was fluorescent.

Table V. Reaction of 9-Borabicyclo[3.3.1]nonane with Representative Carboxylic Acids and Acyl Derivatives in Tetrahydrofuran at 25 °C[a]

Registry no.	Compd	Time, h	Hydrogen evolved[b]	Hydride used[b]	Hydride used for redn[b]
142-62-1	Hexanoic acid	0.5	1.03		
		6.0	1.03	1.13	0.10
		24.0	1.03	1.38	0.35
		72.0	1.03	1.83	0.80
		6.0[c]	1.03	2.39	1.36
		24.0[c]	1.03	3.13	2.10
65-85-0	Benzoic acid	0.5	1.04	1.04	0.00
		12.0	1.04	1.15	0.11
		24.0	1.04	1.22	0.18
		6.0[c]	1.04	1.84	0.80
108-24-7	Acetic Anhydride	0.5	0.06	1.93	1.87
		1.0	0.06	2.01	1.95
		3.0	0.06	2.01	1.95
		24.0	0.06	2.10	2.04
108-30-5	Succinic anhydride	1.0	0.03	0.35	0.32
		3.0	0.03	0.58	0.55
		24.0	0.03	1.31	1.28
		48.0	0.03	1.70	1.67
85-44-9	Phthalic anhydride	6.0	0.04	0.41	0.37
		24.0	0.04	0.92	0.88
		48.0	0.04	1.52	1.48
142-61-0	Hexanoyl chloride	0.5	0.08	1.63	1.55
		1.0	0.08	1.96	1.88
		3.0	0.08	2.06	1.98
		6.0	0.08	2.08	2.00
98-88-4	Benzoyl chloride	0.5	0.00	0.79	0.79
		1.0	0.00	1.19	1.19
		3.0	0.00	1.86	1.86
		6.0	0.00	2.01	2.01

[a-c] See the corresponding footnotes in Table I.

borneol, respectively) (eq 9). This is comparable to the stereoselectivity achieved with disiamylborane.



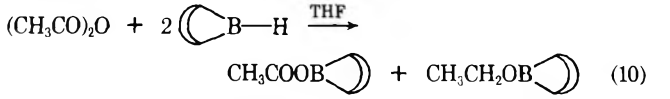
100% (75% exo) (9)

The lower stereoselectivity observed with 9-BBN in these transformations is attributed to two factors: (1) a decrease in the steric crowding around boron attributed to the rigid bicyclic structure; (2) a possible change in the nature of the species involved in the reduction (discussed later).

Quinones. *p*-Benzoquinone rapidly consumed 0.46 hydride per mole of compound of which 85% was utilized for hydrogen evolution and the remaining 15% for reduction, a value which did not change with time. A white, gelatinous precipitate was observed. The value does not correspond either to reduction to hydroquinone or 1,4-dihydroxycyclohexadiene. However, the reaction with anthraquinone is quite simple. It reacts fairly rapidly (3 h) with 2 equiv of reagent, without any hydrogen evolution, to give cleanly 9,10-dihydro-9,10-anthracenediol. Anthraquinone itself is only sparingly soluble in THF. After 2 h all of it went into solution. The results are summarized in Table IV.

Carboxylic Acids and Derivatives. Both hexanoic acid and benzoic acid liberate hydrogen rapidly and quantitatively (<5 min). Further reduction with hexanoic acid is very slow; however, complete reduction can be achieved at 65 °C in 24 h. The corresponding reaction with benzoic acid is very slow.

Acetic anhydride consumes two hydrides very rapidly for reduction with only a slow reduction thereafter, presumably to give ethanol and acetic acid (eq 10). Both succinic anhy-



(10)

dride and phthalic anhydride react only at a moderate rate.

Surprisingly, both hexanoyl chloride and benzoyl chloride undergo reduction utilizing 2 equiv of hydride with remarkable ease (3–6 h). This was quite unexpected since both borane and thexylborane react sluggishly with acid chlorides and disiamylborane is inert. The results are summarized in Table V.

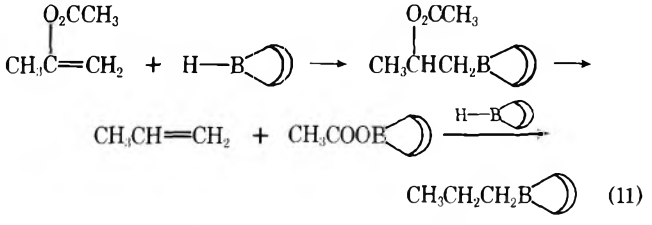
Esters and Lactones. Both ethyl hexanoate and phenyl acetate undergo reduction at a moderate rate and the reduc-

Table VI. Reaction of 9-Borabicyclo[3.3.1]nonane with Representative Esters and Lactones in Tetrahydrofuran at 25 °C[a]

Registry no.	Compd	Time, h	Hydrogen evolved[b]	Hydride used[b]	Hydride used for redn[b]
123-66-0	Ethyl hexanoate	1.0	0.00	0.09	0.09
		3.0	0.00	0.36	0.36
		6.0	0.00	0.70	0.70
		12.0	0.00	1.15	1.15
		24.0	0.00	1.60	1.60
93-89-0	Ethyl benzoate	24.0	0.00	0.45	0.45
		48.0	0.00	0.68	0.68
122-79-2	Phenyl acetate	24.0	0.10	0.99	0.89
		96.0	0.10	1.78	1.68
		192.0	0.10	2.03	1.93
96-48-0	γ-Butyrolactone	0.5	0.00	0.87	0.87
		1.0	0.00	1.30	1.30
		3.0	0.00	1.85	1.85
		6.0	0.00	2.00	2.00
87-41-2	Phthalide	6.0	0.00	0.71	0.71
		24.0	0.00	1.56	1.56
		48.0	0.00	2.07	2.07
		72.0	0.00	2.08	2.08
591-87-7	Isopropenyl acetate	0.5	0.03	1.60	1.57
		1.0	0.03	1.88	1.85
		3.0	0.03	2.05	2.02
		6.0	0.03	2.08	2.05
		24.0	0.03	2.40	2.37

[a,b] See the corresponding footnotes in Table I.

tion of ethyl benzoate is slow. Ethyl hexanoate can be reduced rapidly in refluxing THF. Of the lactones γ-butyrolactone undergoes reduction at a moderate rate, with an uptake of two hydrides in 6 h. The reduction of phthalide is slow, requiring 48 h. Isopropenyl acetate consumes two hydrides rapidly and the further reduction proceeds only slowly. Presumably the reaction involves an initial hydroboration, followed by rapid elimination and the hydroboration of 1-propene produced in the elimination step (eq 11).



(11)

The results are summarized in Table VI.

Epoxides and Halides. Both *n*-octyl bromide and *p*-bromotoluene are completely inert toward 9-BBN and are recovered essentially in quantitative yield after 24 h. The reactions of 1,2-butylene oxide and cyclohexene oxide with 9-BBN are quite sluggish, requiring 3 and 8 days for completion, respectively (one hydride uptake). Styrene oxide proceeds beyond the utilization of one hydride, revealing 1.36 hydride uptake in 48 h. This is quite similar to the observations made with borane and other alkyl-substituted boranes, attributed to the attack of the aromatic nucleus.[6] The reaction of 1-methylcyclohexene oxide also proceeds slowly, accompanied by hydrogen evolution. One hydride is utilized for hydrogen evolution and one hydride is utilized for reduction, a behavior similar to that observed with borane, thexylborane, and disiamylborane indicating the formation of 2-hydroxymethylcyclohexanol following oxidation.

Although the reaction of epoxides with 9-BBN is quite slow, introduction of a catalytic amount of lithium borohydride has a dramatic effect on the rate of the reaction. Thus in the presence of 7.5 mol % of lithium borohydride, 1,2-butylene oxide is reduced completely in 30 min at 25 °C to give 98% of butanols (98% of 2- and 2% of 1-butanol).[14] Thus, the 9-BBN–borohydride combination provides yet another method for the rapid reduction of the epoxides. The results are summarized in Table VII.

Amides and Nitriles. Primary amides react to liberate only one of the two possible hydrogens; while the hydrogen evolution with the benzamide is complete in 0.5 h, hexanamide requires 24.0 h. Further reduction of benzamide is very slow. Hexanamide consumes one hydride at a moderate rate in 48 h and no further reduction is observed. Both the tertiary amides undergo rapid reduction consuming two hydrides to give alcohols as the major product. Reaction with nitriles is sluggish. However, in refluxing tetrahydrofuran the reduction of hexanenitrile is complete in 24 h. The results are summarized in Table VIII.

Nitro Compounds and Their Derivatives. 1-Nitropropane is inert to 9-BBN. However, nitrobenzene is reduced very slowly. Azobenzene is completely inert whereas azoxybenzene undergoes reduction, presumably to azobenzene, consuming two hydrides, one for the hydrogen evolution and the other for reduction. These results are similar to those observed with disiamylborane. The results are summarized in Table IX.

Other Nitrogen Compounds. Cyclohexanone oxime liberates one hydrogen rapidly and then slowly utilizes one hydride for reduction slowly (3 days), indicating reduction to the *N*-cyclohexylhydroxylamine. Phenyl isocyanate consumes two hydrides rapidly, with consumption of a third hydride proceeding sluggishly. Pyridine undergoes very slow reduction. Pyridine *N*-oxide utilizes two hydrides in total, 0.34 hydride for the hydrogen evolution and 1.67 hydride for the reduction. Borane and thexylborane liberate no hydrogen, consuming three hydrides at a moderate rate. Disiamylborane reduction utilizes two hydrides, one for the hydrogen evolution and the other for reduction. Based on these, we are now in a position to offer plausible explanations (Scheme I). The results are summarized in Table X.

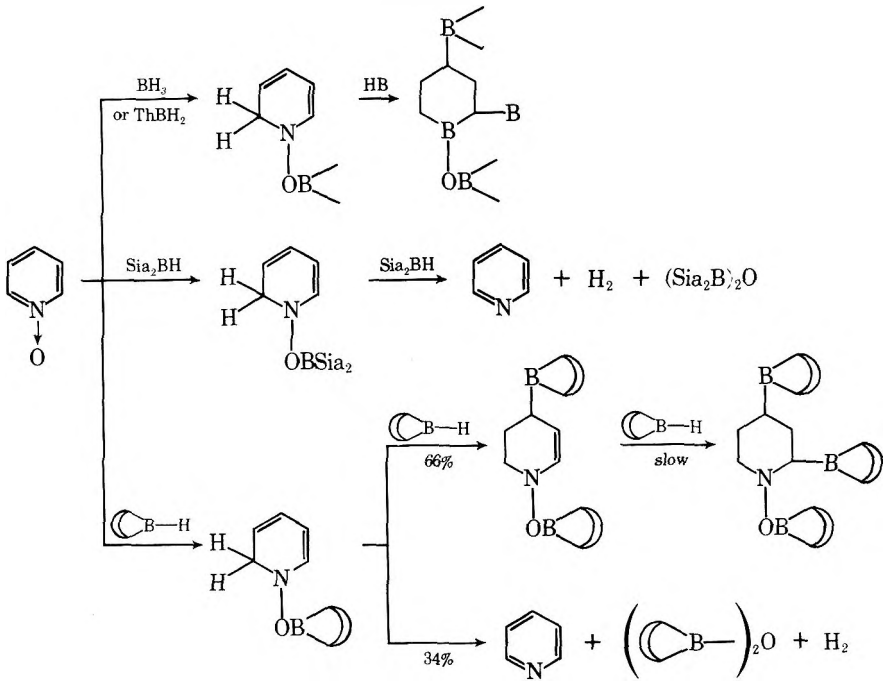
Sulfur Compounds. Among the sulfur compounds examined only dimethyl sulfoxide was reduced (presumably to dimethyl sulfide) by 9-BBN consuming one hydride for hydrogen evolution and one hydride for reduction. Both

Table VII. Reaction of 9-Borabicyclo[3.3.1]nonane with Representative Halides and Epoxides in Tetrahydrofuran at 25 °C[a]

Registry no.	Compd	Time, h	Hydrogen evolved[b]	Hydride used[b]	Hydride used for redn[b]
111-83-1	*n*-Octyl bromide	3.0	0.00	0.00	0.00
		12.0	0.00	0.00	0.00
		24.0	0.00	0.00	0.00
106-38-7	*p*-Bromotoluene	3.0	0.00	0.00	0.00
		12.0	0.00	0.00	0.00
		24.0	0.00	0.00	0.00
106-88-7	1,2-Butylene oxide	12.0	0.03	0.46	0.43
		24.0	0.03	0.67	0.64
		48.0	0.03	0.86	0.83
		96.0	0.03	1.04	1.01
286-20-4	Cyclohexene oxide	3.0	0.00	0.10	0.10
		6.0	0.00	0.17	0.17
		12.0	0.00	0.24	0.24
		24.0	0.00	0.43	0.43
96-09-3	Styrene oxide	1.0	0.03	0.21	0.18
		6.0	0.03	0.80	0.77
		24.0	0.03	1.13	1.10
		48.0	0.03	1.39	1.36
1713-33-3	1-Methylcyclohexene oxide	12.0	0.81	1.36	0.65
		24.0	0.90	1.66	0.76
		48.0	0.96	1.92	0.96
		72.0	1.03	2.00	0.97

[a,b] See the corresponding footnotes in Table I.

Scheme I



methanesulfonic acid and *p*-toluenesulfonic acid liberated hydrogen quantitatively. However, no reduction was observed. Disulfide, sulfide, sulfone, and cyclohexyl tosylate were all inert to 9-BBN. These observations are very similar to those previously realized with borane, thexylborane, and disiamylborane. The results are summarized in Table XI.

Mechanistic Considerations. Kinetics of the Reaction of 9-Borabicyclo[3.3.1]nonane with Representative Substrates. Mode of Action of 9-BBN. Our preliminary exploration of the reaction of 9-BBN with hydroxylic compounds revealed certain interesting features. For example, the reactions of excess 9-BBN with simple alcohols such as methanol, ethanol, *tert*-butyl alcohol, and 3-ethyl-3-pentanol did not exhibit any significant difference in their rates. The reactions of 9-BBN with a stoichiometric quantity of methanol, 1-hexanol, 3-hexanol, etc., were also quite insensitive to the structure of the alcohol, requiring 1 h for completion. This was puzzling. The rates of reactions of disiamylborane with various alcohols have been studied.[6b] Hydrogen evolution was instantaneous with primary and secondary alcohols. However, no hydrogen evolution was observed with the tertiary alcohol, 3-ethyl-3-pentanol. Consequently, 9-BBN is evidently less sterically hindered than disiamylborane.

How can we account for the slower rates of reactions of 9-BBN with simple alcohols? Presumably, the sluggish reaction of 9-BBN with simple alcohols may be a reflection of the unusual stability of the boron–hydrogen bridge in the 9-BBN dimer. It would be desirable to have an understanding of the mechanism of these reactions which would provide a reasonable explanation for the marked difference in the behavior of 9-BBN and Sia_2BH.

Accordingly, we undertook to measure precisely the rates

Table VIII. Reaction of 9-Borabicyclo[3.3.1]nonane with Representative Amides and Nitriles in Tetrahydrofuran at 25 °C[a]

Registry no.	Compd	Time, h	Hydrogen evolved[b]	Hydride used[b]	Hydride used for redn[b]
628-02-4	Hexanamide	3.0	0.62	1.29	0.67
		6.0	0.68	1.38	0.70
		24.0	0.96	1.74	0.78
		48.0	0.98	2.02	1.04
55-21-0	Benzamide	3.0	1.01	1.01	0.00
		24.0	1.12	1.18	0.06
5830-30-8	*N,N*-Dimethyl-hexanamide	1.0	0.25	1.88	1.63
		3.0	0.27	2.12	1.85
611-74-5	*N,N*-Dimethyl-benzamide	0.25	0.00	1.35	1.35
		1.0	0.00	1.98	1.98
		3.0	0.00	2.00	2.00
		6.0	0.00	2.01	2.01
628-73-9	Hexanenitrile	3.0	0.00	0.10	0.10
		6.0	0.00	0.22	0.22
		24.0	0.00	0.40	0.40
		48.0	0.00	0.88	0.88
		3.0[c]	0.00	1.43	1.43
		6.0[c]	0.00	1.74	1.74
		24.0[c]	0.00	2.16	2.16
100-47-0	Benzonitrile	1.0	0.00	0.23	0.23
		3.0	0.00	0.36	0.36
		24.0	0.00	0.74	0.74
		48.0	0.00	0.78	0.78
		3.0[c]	0.01	1.04	1.03
		6.0[c]	0.01	1.23	1.22
		24.0[c]	0.01	1.55	1.54
		48.0[c]	0.01	1.60	1.59

[a,b] See the corresponding footnotes in Table I. [c] Refluxing THF.

Table IX. Reaction of 9-Borabicyclo[3.3.1]nonane with Nitro Compounds and Their Derivatives in Tetrahydrofuran at 25 °C[a]

Registry no.	Compd	Time, h	Hydrogen evolved[b]	Hydride used[b]	Hydride used for redn[b]
108-03-2	1-Nitropropane	1.0	0.00	0.00	0.00
		12.0	0.00	0.00	0.00
98-95-3	Nitrobenzene	1.0	0.00	0.00	0.00
		12.0	0.00	0.00	0.04
		24.0	0.00	0.08	0.08
103-33-3	Azobenzene	1.0	0.00	0.02	0.02
		24.0	0.00	0.02	0.02
495-48-7	Azoxybenzene	24.0	0.66	1.32	0.66
		72.0[c]	0.86	1.89	1.03
		96.0[c]	0.91	2.00	1.09

[a,b] See corresponding footnotes in Table I. [c] Solution color changed from light yellow to orange.

Table X. Reaction of 9-Borabicyclo[3.3.1]nonane with Other Nitrogen Compounds in Tetrahydrofuran at 25 °C[a]

Registry no.	Compd	Time, h	Hydrogen evolved[b]	Hydride used[b]	Hydride used for redn[b]
100-64-1	Cyclohexanone oxime	6.0	1.01	1.27	0.26
		24.0	1.01	1.77	0.76
		36.0	1.01	1.86	0.85
		86.0	1.01	2.04	1.03
103-71-9	Phenyl isocyanate	0.5	0.01	1.76	1.75
		1.0	0.01	2.00	1.99
		24.0	0.01	2.29	2.28
110-86-1	Pyridine[c]	1.0	0.00	0.06	0.06
		24.0	0.00	0.09	0.09
694-59-7	Pyridine *N*-oxide[c]	1.0	0.21	0.53	0.32
		3.0	0.32	1.19	0.87
		12.0	0.34	1.75	1.49
		24.0[d]	0.34	1.87	1.53
		48.0	0.34	2.01	1.67

[a,b] See the corresponding footnotes in Table I. [c] Yellow color was observed when compound was added. [d] Solution became colorless.

Table XI. Reaction of 9-Borabicyclo[3.3.1]nonane with Representative Sulfur Derivatives in Tetrahydrofuran at 25 °C[a]

Registry no.	Compd	Time, h	Hydrogen evolved[b]	Hydride used[b]	Hydride used for redn[b]
629-45-8	Di-*n*-butyl disulfide	1.0	0.00	0.00	0.00
		6.0	0.00	0.00	0.00
		24.0	0.00	0.00	0.00
882-33-7	Diphenyl disulfide	1.0	0.00	0.00	0.00
		6.0	0.00	0.02	0.02
		48.0	0.00	0.01	0.01
623-13-2	Methyl *p*-tolyl sulfide	1.0	0.00	0.00	0.00
		6.0	0.00	0.02	0.02
		24.0	0.00	0.04	0.04
67-68-5	Dimethyl sulfoxide	6.0	0.34	0.63	0.29
		24.0	0.76	1.51	0.75
		48.0	0.96	1.94	0.98
		72.0	1.00	2.00	1.00
127-63-9	Diphenyl sulfone	1.0	0.01	0.02	0.01
		6.0	0.01	0.02	0.01
		48.0	0.01	0.03	0.02
75-75-2	*Methanesulfonic acid*	0.5	1.07	1.07	0.00
		48.0	1.07	1.07	0.00
104-15-4	*p*-Toluenesulfonic acid monohydrate	1.0	3.03	3.07	0.04
		24.0	3.03	3.07	0.04
953-91-3	Cyclohexyl tosylate	1.0	0.00	0.00	0.00
		12.0	0.00	0.00	0.00

[a,b] See the corresponding footnotes in Table I.

Table XII. Rates of Reaction of 9-Borabicyclo[3.3.1]nonane with Various Substrates in Tetrahydrofuran at 25 ± 0.5 °C

			Reaction, %												First order
Compd	M	M	2 min	4 min	5 min	8 min	10 min	12 min	15 min	20 min	25 min	30 min	45 min	60 min	$10^{-3}k_1$, s^{-1}
Methanol[a]	0.2	0.1	33	45	50	62	69	74	80	88	92	95	98	99	1.56
	0.4	0.1	33	41	50	61	68	74	80	87	91	95			1.52
Methanol-*O*-*d*[a]	0.2	0.1	32	44	48	61	69	73	80	87	91	94			1.53
1-Hexanol[a]	0.2	0.1	32	42	47	59	65	70	76	85	90	93	96	98	1.39
	0.4	0.1	31	41	47	57	65	71	79	85	90	93	98		1.44
	0.6	0.1	32	42	47	57	63	67	74	82	88	91	97	98	1.24
3-Hexanol[a]	0.2	0.1	31	43	48	59	66	70	77	86	90	95	98		1.42
	0.4	0.1	30	42	46	59	65	70	77	83	89	92			1.34
Hexanoic acid[a]	0.25	0.125	32	44	48	60	66	73	79	85	91	95	99		1.77
	0.50	0.125	32	42	47	58	65	70	77	85	90	94	98		1.37
Methanesulfonic acid[a]	0.2	0.1	34	44	50	61	67	73	79	86	92	95	98		1.46
	0.4	0.1	34	44	50	61	67	73	78	86		93	98		1.44
Cyclohexanone[b]	0.2	0.1	32	43	48	57	61		73						1.15
	0.4	0.1	34		49	58	64								1.22
Cyclopentene[c]	0.2	0.1		36		51		59		75					1.06
	0.4	0.2													1.07

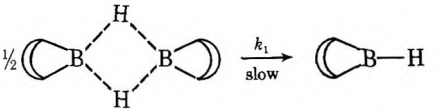
[a] Reaction was monitored by measuring the hydrogen evolved with time. [b] Monitored by GLC using an internal standard. [c] Data taken from ref 5c.

of reactions of 9-BBN with various proton sources as well as with other typical functional groups, such as ketones and olefins at 25 ± 0.5 °C at various concentrations. The results are summarized in Table XII.

It is clearly evident that methanol, 1-hexanol, and 3-hexanol, alcohols in the order of increasing steric requirements, all protonolyze 9-BBN at essentially the comparable rates. Even stronger acids, such as methanesulfonic acid and hexanoic acid, protonolyze 9-BBN, at essentially the same rate. Increasing the concentration of the proton source two- or threefold did not alter the rate. Even more important is the observation that the rate of reaction of cyclohexanone and the rate of hydroboration of reactive olefins, such as cyclopentene, with 9-BBN are comparable to the protonolysis rate. These rates also were independent of the reactant concentration. All of these reactions gave excellent first-order kinetic plots.

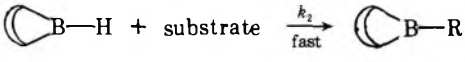
It was previously pointed out that 9-BBN exists as an exceptionally tightly bound dimer in solid as well as in solution. Thus, the above experimental observations can be attributed to the following steps (eq 12 and 13).

(a) A slow rate-determining dissociation of the dimer to the monomer.



(12)

(b) Rapid capture of the monomer by reactive substrates.



(13)

Consequently, we must be measuring the rate of dissociation of dimer to the monomer, and dimeric 9-BBN does not react. This is in contrast to the behavior of disiamylborane.

Table XIII. Relative Reactivities of Various Functional Groups toward 9-Borabicyclo[3.3.1]nonane in Tetrahydrofuran at 25 °C[a]

Expt	Compd used	mmol	9-BBN, mmol	Products[b]	Mol %	K_{rel}[c]
1	Hexanal	5.0		Hexanal	5.0	
			5.0	1-Hexanol	44.3	27.0
	2-Heptanone	5.0		2-Heptanone	45.9	
				2-Heptanol	3.8	
2	Cyclohexanone	5.0		Cyclohexanone	23.5	
			5.0	Cyclohexanol	26.5	1.2
	Methanol	5.0		Methanol	26.8	
				B-Methoxy-9-BBN	23.2	
3	Cyclohexanone	5.0		Cyclohexanone	25.0	
			5.0	Cyclohexanol	25.5	1.1
	2-Cyclohexen-1-one	5.0		2-Cyclohexen-1-one	27.0	
				2-Cyclohexen-1-ol	22.5	
4	Cyclohexanone	5.0		Cyclohexanone	15.0	
			5.0	Cyclohexanol	37.0	
	Cyclopentanone	5.0		Cyclopentanone	34.5	3.2
				Cyclopentanol	13.0	
5	Cyclohexanone	5.0		Cyclohexanone	6.0	
			5.0	Cyclohexanol	43.5	
	Cyclopentene	5.0		Cyclopentene	47.3	37.5
				B-Cyclopentyl-9-BBN	3.2	
6	Cyclopentene	5.0		Cyclopentene	1.5	
			5.0	*B*-Cyclopentyl-9-BBN	50.0	
	Ethyl hexanoate	5.0		Ethyl hexanoate	50.0	
				1-Hexanol	0.0	
7	Cyclopentene	5.0		Cyclopentene	5.5	
			10.0	*B*-Cyclopentyl-9-BBN	43.5	
	Caproic acid[d]	5.0		Caproic acid[e]	49.0	
				1-Hexanol	1.0	
8	Cyclopentene	5.0		Cyclopentene	2.5	
			5.0	*B*-Cyclopentyl-9-BBN	50.0	
	Epoxycyclohexane	5.0		Epoxycyclohexane	46.5	
				Cyclohexanol	0.0	
9	Hexanoyl chloride	5.0		Hexanoyl chloride[e]	<2.5	
			10.5	1-Hexanol	47.5	
	Methyl heptanoate	5.0		Methyl heptanoate	49.8	
				1-Heptanol	<0.1	
10	Hexanoyl chloride	5.0		Hexanoyl chloride[e]	5.5	
			10.0	1-Hexanol	44.5	
	2-Hexyl acetate	5.0		2-Hexyl acetate	49.0	
				2-Hexanol	<1.0	

[a] Unless otherwise indicated, reaction mixtures were 0.2 M in both 9-BBN and the substrates. [b] Analysis by GLC using an internal standard. [c] $K_{rel} = k_A/k_B$. [d] An additional 1 equiv of 9-BBN was used to correct for quantitative hydrogen evolution, 9-BBN concentration 0.4 M. [e] Not determined directly; estimated by difference.

Kinetics of the hydroboration of olefins with disiamylborane indicate the dimer to be the hydroborating agent, not the monomer.[15] Accordingly, this is the basis for differences observed with Sia_2BH and 9-BBN. Further, protonolysis of 9-BBN with methanol and methanol-*O*-*d* shows no significant difference in their rates ($k_{MeOH}/k_{MeOD} = 1.02$), indicating that O–H bond breaking is not involved in the rate-determining step, supporting the above mechanism.

Finally, the above mechanism suggests that if two rapidly reacting substrates of different reactivities are allowed to compete for the limited quantity of 9-BBN, then the monomer 9-BBN should be able to distinguish them. Indeed, $k_{cyclohexanone}/k_{cyclopentene}$ was found to be 37.5 (discussed in the next section) when the reaction was carried out in the same flask as a competitive reaction; when the relative reactivities were compared kinetically, the ratio was 1.08.

Relative Reactivity Studies. Competition Experiments. Extensive study of the reaction of typical organic functional groups with 9-BBN gave a rough indication of the relative ease of reduction by this reagent of representative functional groups.

However, functional groups which react rapidly with 9-BBN did not show any significant difference in their reactivity, since dissociation of the dimer is the rate-determining step. Consequently, it was desirable to examine the relative reactivities of certain functional groups by means of competition experiments. Accordingly, equimolecular amounts of two compounds containing representative functional groups were allowed to compete for a limited quantity of 9-BBN in THF. The 9-BBN was added slowly to the reaction mixture maintained at 25 °C. After appropriate time intervals, the mixture was analyzed by GLC using an internal standard. The results are summarized in Table XIII.

The competitive reduction of a mixture of hexanal and 2-heptanone resulted in the preferential reduction of the aldehyde of over 85% ($k_{hexanal}/k_{2\text{-heptanone}} = 27$). The reactivity of ketone and alcohol are essentially identical as evident from the cyclohexanone–methanol pair ($k_{cyclohexanone}/k_{methanol} = 1.2$). Further, there is no significant difference between conjugated 2-enones and a saturated ketone ($k_{cyclohexanone}/k_{2\text{-cyclohexenone}} = 1.1$). Cyclohexanone is reduced at a faster rate than cyclopentanone by a factor of 3.2.

The ease of reduction of aldehydes and ketones by this reagent is remarkable. Thus, 9-BBN reacts with cyclohexanone in preference to cyclopentene ($k_{cyclohexanone}/k_{cyclopentene} = 37.5$). This is complementary to the behavior of borane, which

exhibits greater reactivity toward olefins. This led to the detailed systematic exploration of 9-BBN for the selective reduction of α,β-unsaturated aldehydes and ketones to the corresponding allylic alcohols.[16]

Cyclopentene reacts completely to the total exclusion of an ester, an acid, and an epoxide.

Finally, acid chlorides are reduced rapidly and preferentially without any significant attack on the esters (≤2%).

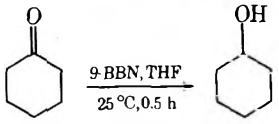
With certain pairs the relative reactivity $k_{rel} = k_A/k_B$ was calculated using the expression of Ingold and Shaw.[17]

$$k_{rel} = \frac{\log A_0 - \log A}{\log B_0 - \log B}$$

Synthetic Utility. In order to establish the synthetic utility of this new reducing agent product studies for the reduction of selected compounds containing representative functional groups were carried out. We utilized essentially stoichiometric quantity of 9-BBN (as defined by stoichiometric studies) with most of the functional groups examined. With carboxylic acids, a modest excess of 9-BBN, 4.00 9-BBN per mole of RCOOH (33% excess), was utilized. Reductions were carried out either at 25 or 65 °C (refluxing THF) depending upon the ease with which the functional group undergoes reduction. As already discussed earlier, the products were identified by GLC or by isolation.

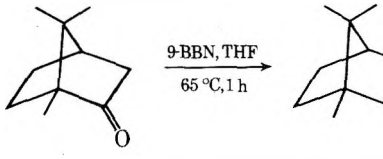
Simple aldehydes and ketones such as hexanal, cyclohexanone, 2-methylcyclohexanone, etc., were reduced rapidly to their corresponding alcohols in excellent yield (>95%) (eq 14 and 15). Even the hindered ketone camphor was reduced

$$CH_3(CH_2)_4CHO \xrightarrow[25\ °C,1\ h]{9\text{-BBN, THF}} CH_3(CH_2)_4CH_2OH\ 100\% \quad (14)$$



100% (78% isolated) (15)

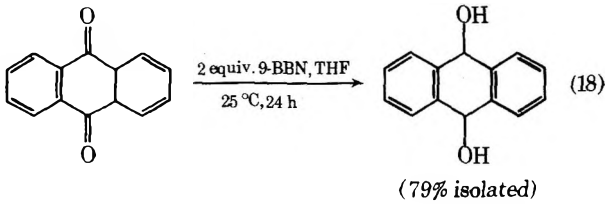
to borneols in quantitative yield in 12 h at 25 °C. In refluxing THF the complete reduction can be achieved in 1 h (eq 16). Cinnamaldehyde was converted into cinnamyl alcohol in 98% yield (eq 17).



100% (81% isolated) (16)

$$C_6H_5CH{=}CH{\cdot}CHO \xrightarrow[0\ °C,2\ h]{9\text{-BBN, THF}} C_6H_5CH{=}CHCH_2OH\ 98\% \quad (17)$$

Anthraquinone was converted into 9,10-dihydro-9,10-anthracenediol in 79% yield (eq 18).



(18)

(79% isolated)

Carboxylic acids such as *n*-hexanoic acid and *n*-octanoic acid were converted into *n*-hexyl alcohol and *n*-octyl alcohol, respectively, in 92% yield in refluxing THF (eq 19).

$$CH_3(CH_2)_6COOH \xrightarrow[65\ °C,18\ h]{4\ \text{equiv. 9-BBN, THF}} CH_3(CH_2)_6CH_2OH \quad (19)$$

92% (83% isolated)

Acid chlorides, such as hexanoyl chloride and benzoyl chloride, were converted into *n*-hexyl alcohol and benzyl alcohol in yields of 92 and 90%, respectively (eq 20).

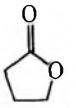
$$CH_3(CH_2)_4COCl \xrightarrow[25\ °C,12\ h]{2\ \text{equiv. 9-BBN, THF}} CH_3(CH_2)_4CH_2OH \quad (20)$$

92% (81% isolated)

Esters such as ethyl hexanoate and methyl heptanoate were reduced in reflux using THF to 1-hexanol and 1-heptanol in yields of 100 and 99%, respectively (eq 21). γ-Butyrolactone was reduced to 1,4-butanediol in 98% yield (eq 22).

$$CH_3(CH_2)_5COOCH_3 \xrightarrow[65\ °C,4\ h]{2\ \text{equiv. 9-BBN, THF}} CH_3(CH_2)_5CH_2OH \quad (21)$$

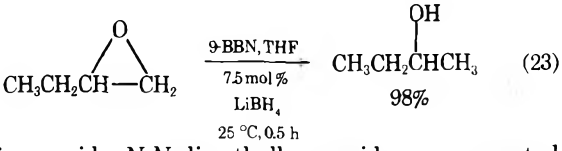
99% (77% isolated)



$$\xrightarrow[65\ °C,2\ h]{2\ \text{equiv. 9-BBN, THF}} HOCH_2CH_2CH_2CH_2OH \quad (22)$$

98%

Epoxides such as 1,2-butylene oxide reacted sluggishly with 9-BBN alone, but were reduced quantitatively in the presence of a catalytic quantity of $LiBH_4$ (eq 23).



(23)

Tertiary amide, *N,N*-dimethylbenzamide, was converted into benzyl alcohol and *N,N*-dimethylbenzylamine (eq 24). The results are summarized in Table XIV.

$$C_6H_5CON(CH_3)_2 \xrightarrow[25\ °C,4\ h]{9\text{-BBN, THF}} \underset{80\%}{C_6H_5CH_2OH} + \underset{20\%}{C_6H_5CH_2N(CH_3)_2} \quad (24)$$

Scope and Applicability. Detailed and systematic explorations on the reducing characteristics of 9-BBN have revealed many interesting and unusual features of this reagent, quite different from those observed for borane and other partially alkylated boranes previously studied. The reactivity of various functional groups toward 9-BBN can be classified into five broad categories as follows: (1) very rapid reduction—aldehyde and ketone; (2) rapid reduction—olefin, quinone, tertiary amide, acid anhydride, acid chloride, and lactone; (3) slow reduction—ester, epoxide, and oxime; (4) very slow reduction—carboxylic acid, sulfoxide, and azoxy; (5) inert (no reaction)—nitro (both aliphatic and aromatic), azo, sulfide, disulfide, sulfone, sulfonic acid, tosylate, halogen (aryl and alkyl).

9-BBN has four major advantages over borane and other partially alkylated boranes. First, solid 9-BBN is relatively insensitive to air and can be handled with no more hazard than lithium aluminum hydride. Second, as solid and solution, it is indefinitely stable. One such solution prepared in THF did not lose any of its activity even after 6 years. Third, unlike BH_3–THF and other dialkylboranes, its thermal stability is exceptional. This permits the reduction of even difficultly reducible groups, such as carboxylic acids. Fourth, 9-BBN is soluble in a variety of organic solvents.

Reduction of aldehydes and ketones with 9-BBN proceeds rapidly and quantitatively. Consequently, this permits the ready reduction of such groups in the presence of almost any other functional group listed in the categories 2–5. The feasibility of utilizing elevated temperatures with this reagent renders possible the smooth reduction of even hindered ketones such as camphor in a short period (1 h, 65 °C).

Selective reduction of α,β-unsaturated aldehydes and ketones to the corresponding allylic alcohols represents one of the major application of this new reducing agent. Indeed, a detailed study underway in our laboratory has revealed a considerable number of interesting applications of this reagent for this purpose (especially with the functionalized α,β-unsaturated system[16]).

Table XIV. Products of Reduction of Selected Organic Compounds Containing Representative Functional Groups with 9-Borabicyclo[3.3.1]nonane in Tetrahydrofuran

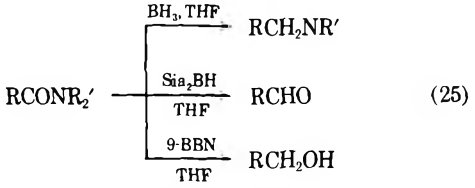
Compd	Time, h	Temp, °C	Ratio 9-BBN/compd	Products	Yield,[a] %
Hexanal	0.5	25	1.0	1-Hexanol	100
Cyclohexanone	1.0	25	1.0	Cyclohexanol	100 (78)
2-Methylcyclohexanone	1.0	25	1.0	2-Methylcyclohexanol	100
2,2,4,4-Tetramethyl-3-pentanone	24.0	65	4.0	2,2,4,4-Tetramethyl-3-pentanol	<1.0
				2,2,4,4-Tetramethyl-3-pentanone	96
Camphor	12.0	25	1.0	Borneols	100
	1.0	65	1.0	Borneols	100 (81)
Cinnamaldehyde	2.0	0	1.0	Cinnamyl alcohol	98
Anthraquinone	24.0	25	2.0	9,10-Dihydro-9,10-anthracenediol	(79)
Hexanoic acid	18.0	65	4.0	1-Hexanol	92
Octanoic acid	18.0	65	4.0	1-Octanol	92 (83)
Benzoyl chloride	6.0	25	4.0	Benzyl alcohol	90
Hexanoyl chloride	18.0	25	2.0	1-Hexanol	92 (81)
Ethyl hexanoate	24.0	25	4.0	1-Hexanol	75
	4.0	65	2.0	1-Hexanol	100
Methyl heptanoate	4.0	65	2.0	1-Heptanol	99 (77)
γ-Butyrolactone	2.0	65	2.0	1,4-Butanediol	98
Cyclohexene oxide	24.0	25	4.0	Cyclohexanol	30
1,2-Butylene oxide	0.5	25	4.0	2-Butanol	98
				1-Butanol	2
n-Octyl bromide	24.0	25	4.0	*n*-Octane	0
				n-Octyl bromide	100
p-Bromotoluene	24.0	25	4.0	Toluene	0
				p-Bromotoluene	96
N,N-Dimethylbenzamide	3.0	25	4.0	Benzyl alcohol	80
				N,N-Dimethylbenzylamine	20
Nitrobenzene	24.0	25	4.0	Nitrobenzene	90
Di-*n*-butyl disulfide	24.0	25	4.0	Di-*n*-butyl disulfide	98

[a] Yields were determined by GLC using a suitable internal standard. Numbers in parentheses indicate the isolated yield.

The facile and clean reduction of anthraquinone to 9,10-dihydro-9,10-anthracenediol in 79% yield represents another promising area of application, useful in the area of synthetic dyes. Currently available hydride reducing agents, such as lithium aluminum hydride and its alkoxy derivatives, borane–THF, etc., yield a mixture of 9,10-dihydro-9,10-anthracenediol and 9,10-dihydroxyanthracene.[6,18]

The rapid and quantitative reduction of acid chlorides with 9-BBN provides a convenient entry to the corresponding alcohols. This was quite unexpected since borane and disiamylborane are inert to acid chlorides and thexylborane reacts only sluggishly.[6] Even more important is the observation that the acid chlorides can be selectively reduced in the presence of esters, with no significant attack on the ester group. No other hydride reagent currently available exhibits such a unique selectivity.

The reduction of tertiary amides to alcohols represents yet another promising area of applications that requires detailed exploration. It should be pointed out that the reduction with borane–THF proceeds to give amines and with disiamylborane yields aldehydes. Consequently, we are now in a position to control the course of this reaction using various reagents to get three different products (eq 25).



(25)

Recently, 9-BBN has been found to exhibit good selectivity for the γ-carboxyl group of the glutamate and unhindered C-terminal carboxylate group with only marginal reduction of the β-carboxyl group of aspartate in proteins.[19] Borane–THF also reduces the carboxyl groups in proteins, but will not differentiate between γ-, β-, and C-terminal carboxyl groups.[20] Further, unlike BH_3–THF, 9-BBN does not cleave the disulfide bonds which are responsible for the tertiary structure of the protein (and their enzymatic activity). Consequently, 9-BBN should be highly useful for the specific chemical modification of proteins and as a valuable conformational probe.

Conclusions

9-Borabicyclo[3.3.1]nonane hydroborates olefins with very high regio- and stereoselectivity, thus providing a convenient route to the synthesis of various 9-alkyl-9-BBN derivatives. These derivatives are finding numerous applications in the synthesis of carbon structures. The subject of the present study, the reducing characteristics of 9-BBN, reveals that 9-BBN is also a highly selective and unique reducing agent and should find major applications in organic synthesis.

Experimental Section

Materials. Tetrahydrofuran was dried with excess lithium aluminum hydride, distilled under nitrogen, and stored over 5-Å molecular sieves. Borane solution in THF was prepared from sodium borohydride and boron trifluoride etherate and standardized by hydrolyzing a known aliquot of the solution with glycerine–water–THF mixture and measuring the hydrogen evolved.[21,22]

Most of the organic compounds utilized in this study were the commercial products of the highest purity. They were further purified by distillation or recrystallization when necessary. Some compounds were synthesized using standard procedures. In all of the cases, physical constants agreed satisfactorily with constants in the literature. All glassware was dried thoroughly in a drying oven and cooled under a dry stream of nitrogen. All reduction experiments were carried out under a dry nitrogen atmosphere. Hypodermic syringes were used to transfer the solution.[23]

Standard Solution of 9-Borabicyclo[3.3.1]nonane in Tetrahydrofuran.[5b,c] A 2-l. flask, oven dried, equipped with a side arm

fitted with a silicone rubber stopple, was cooled down under a dry stream of nitrogen. It was fitted with a magnetic stirring bar and a reflux condenser connected to a mercury bubbler. The flask was maintained under a static nitrogen pressure and immersed in an ice bath (ca. 0 °C). Into the flask was introduced 338 ml (800 mmol) of 2.36 M borane solution in THF. After 15 min, 86.4 g (98 ml, 800 mmol) of 1,5-cyclooctadiene was added dropwise with vigorous stirring over a period of 1 h. The ice bath was removed and the mixture was refluxed for 1 h. Then it was cooled to room temperature and 9-BBN crystallized out as a white solid.

9-BBN was purified by repeatedly washing with *n*-pentane (freshly distilled over $LiAlH_4$) at −10 °C. After drying at 50 °C in vacuo, a snow-white solid of 9-BBN was obtained, 73.5 g (75%), mp 152.5–153.5 °C. This was dissolved in 900 ml of THF. The concentration was determined by hydrolyzing 5-ml aliquot solutions with THF–MeOH mixture at 25 °C and measuring the hydrogen evolved (requires 45 min). It was found to be 0.67 M in 9-BBN.

Alternatively, commercial 9-BBN powder was dissolved in THF to give the solutions of required concentration.[7]

Procedure for Rate and Stoichiometry. Reduction of ethyl hexanoate is representative. A 100-ml flask was dried in an oven and cooled down in a dry stream of nitrogen. The flask was equipped with a rubber syringe cap, a magnetic stirring bar, and a reflux condenser connected to a gas buret through a dry ice trap. The flask was immersed in a water bath (ca. 25 °C) and 1.7 ml of THF was introduced into the reaction flask, followed by 35.7 ml (20 mmol) of 0.56 M solution of 9-BBN in THF and 0.57 ml (2.5 mmol) of *n*-dodecane to serve as the internal standard. Finally, 2 ml (5 mmol) of 2.5 M solution of ethyl hexanoate in THF was injected into the reaction flask. Now the reaction mixture was 0.5 M in 9-BBN and 0.125 M in ester. No hydrogen evolution was observed.

At the end of 3 h, an 8.0-ml aliquot of the reaction mixture (1 mmol of the compound) was removed with a hypodermic syringe and injected into a hydrolyzing mixture of THF–MeOH (1:1). The hydrogen evolved was measured. This indicated that 0.36 mmol of hydride had reacted per millimole of the ester (18% reduction). The reaction was monitored at 6 (35%), 12 (58%), and 24 h (80%).

At the end of 24 h, the remaining mixture was hydrolyzed, oxidized, and analyzed on a 5% Carbowax 20M column, 6 ft × 0.125 in., indicating the presence of 75% *n*-hexyl alcohol.

The results for other compounds are summarized in Tables I–XI.

Representative Procedure for Product Analysis by GLC. Reduction of Methyl Heptanoate to 1-Heptanol. A clean, oven-dried, 25-ml flask, equipped with a side arm fitted with a silicone rubber stopple, a magnetic stirring bar, and a reflux condenser connected to a mercury bubbler, was cooled down to room temperature with nitrogen. Then 10.1 ml (5.5 mmol) of a 0.55 M solution of 9-BBN in THF was injected into the reaction flask, followed by 0.285 ml (1.25 mmol) of *n*-dodecane as the internal standard. The flask was heated carefully to reflux temperature. Then 2.5 mmol (0.42 ml) of methyl heptanoate was introduced by a syringe. The mixture was stirred well and at appropriate intervals of time the reaction was monitored by GLC: 2 h (93% reaction), 4 h (99% reaction).

At the end of 4 h, the mixture was allowed to cool down to room temperature and the excess hydride destroyed with MeOH. The boronic acid derivative was oxidized by the addition of 2 ml (6 mmol) of 3 N aqueous sodium hydroxide followed by 1.5 ml (13 mmol) of 30% hydrogen peroxide and heating at 50 °C for 1 h. The aqueous layer was saturated with 2 g of potassium carbonate and the dry THF layer was subjected to GLC analysis on 5% Carbowax 20M column, 6 ft × 0.125 in., indicating the presence of 99% 1-heptanol and 1.5% methyl heptanoate.

Similar procedure was employed for examining the stereochemistry of the reduction of cyclic and bicyclic ketones with 9-BBN.

The results for other compounds are summarized in Tables III and XIV.

General Kinetic Procedures. A. Rate of Protonolysis of 9-BBN with Methanol. A 100-ml flask, with a side arm, a magnetic stirring bar, and a reflux condenser connected to an inverted gas buret via a dry ice trap, was flame dried and cooled down to room temperature under a dry stream of nitrogen. The flask was immersed in a water bath (25 ± 0.5 °C). Then 13.9 ml of dry THF was injected into the reaction flask followed by 9.1 ml (5 mmol) of 0.55 M 9-BBN solution in THF. The mixture was stirred for 20 min to equilibrate to the bath temperature. The reaction was initiated by adding 2 ml (5 mmol) of a 2.5 M solution of methanol in THF (a timer started when half the syring was empty). Now the reaction mixture was 0.1 M in 9-BBN dimer and 0.2 M in methanol. Reaction was monitored by measuring the hydrogen evolved with time. After the reaction came to an effective halt (120 min, 130 ml, 5.02 mmol), the infinity reading was taken. The first-order plot gave a good straight line ($k_1 = 1.56 \times 10^{-3}\ s^{-1}$). Additional kinetic runs in which methanol concentrations were increased to 0.4 M (concentration of 9-BBN dimer being the same, 0.1 M) also gave an excellent first-order plot, $k_1 = 1.52 \times 10^{-3}\ s^{-1}$.

An identical run carried out with methanol-*O*-*d* (99.5% + deuterium content), 0.1 M in $(9\text{-BBN})_2$ and 0.2 M in MeOD, gave $k_1 = 1.53 \times 10^{-3}\ s^{-1}$; $k_{MeOH}/k_{MeOD} = 1.02$.

B. Rate of Reduction of Cyclohexanone with 9-BBN. The experimental setup was the same as in the previous experiments. To the reaction flask was added 27.9 ml of dry THF, followed by 18.1 ml (10 mmol) of 0.55 M solution of 9-BBN in THF. The mixture was stirred for 30 min and allowed to equilibrate to the bath temperature (25.0 ± 0.5 °C). The reaction was initiated by rapidly injecting 4 ml of the THF solution containing 10 mmol of cyclohexanone and 5 mmol of *n*-dodecane (internal standard) into the reaction flask. Now the reaction mixture was 0.1 M in 9-BBN dimer and 0.2 M in cyclohexanone. Samples (5 ml) were withdrawn periodically via syringe and injected into separate flasks containing 3 ml of MeOH + 3 ml of THF to quench the reaction.[24] After stirring for at least 1 h, quenched samples were oxidized with $NaOH–H_2O_2$ and analyzed by GLC on a 5% Carbowax 20M column, 6 ft × 0.125 in., for the remaining cyclohexanone and cyclohexanol formed. The contents of the main reaction flask were stirred for 6 h, then hydrolyzed, oxidized, and analyzed for infinity reading. Reaction gave a good first-order plot, $k_1 = 1.15 \times 10^{-3}\ s^{-1}$. Another experiment performed at 0.4 M cyclohexanone and 0.1 M 9-BBN dimer gave $k_1 = 1.22 \times 10^{-3}\ s^{-1}$.

A similar procedure was employed for measuring the rate of hydroboration of cyclopentene with 9-BBN.[5c]

Competitive Experiments. Reaction of Hexanal and 2-Heptanone with a Limited Quantity of 9-BBN in THF. A typical reaction setup was assembled and the reaction flask was immersed in a water bath (ca. 25 °C). Then 12.7 ml of dry THF was injected into the reaction flask. Hexanal, 5 mmol (0.62 ml, freshly distilled, $n^{20}D$ 1.4035), was added, followed by 2 ml (5 mmol) of 2.5 M solution of 2-heptanone in THF; 0.57 ml (2.5 mmol) of *n*-dodecane was added to serve as an internal standard. The mixture was stirred well and a minute sample withdrawn and analyzed by GLC on a 5% SE-30 column, 8 ft × 0.125 in., for the response ratio of reactants to internal standard. Reaction was initiated by the dropwise addition of 9.2 ml (5 mmol) of 0.54 M 9-BBN solution, over a period of 10 min. The resulting solution (0.2 M in each component and 9-BBN) was stirred well. After 4 h, the mixture was again analyzed, indicating the presence of 0.5 mmol of hexanal and 4.59 mmol of 2-heptanone. Then the mixture was oxidized with $NaOH–H_2O_2$ and analyzed on a 5% Carbowax 20M column, 6 ft × 0.125 in., indicating the presence of 4.43 mmol of 1-hexanol and 0.38 mmol of 2-heptanol.

The relative reactivity, $k_{rel} = k_{hexanal}/k_{2\text{-heptanone}}$, was calculated to be 27, employing the expression of Ingold and Shaw.[17] The results for the other pairs are summarized in Table XIII.

General Preparative Procedures for the Reduction of Organic Compounds with 9-BBN. A series of organic compounds containing representative functional groups were reduced with 9-BBN and the products were isolated to establish the synthetic utility of the reagent (depending upon the other substituents present, the time required may require an increase or decrease).

A. Simple Ketone. The following procedure for the reduction of cyclohexanone is representative. An oven-dried 100-ml flask with a side arm fitted with a silicone rubber stopple, a magnetic stirring bar, and a reflux condenser connected to a mercury bubbler was cooled down to room temperature under dry nitrogen. Then 40.8 ml (26 mmol) of 0.635 M 9-BBN solution in THF was introduced into the reaction flask followed by 2.6 ml (25 mmol) of cyclohexanone. After 1 h at 25°, 0.5 ml of methanol was added to destroy excess hydride. THF was removed under water aspirator and finally over the vacuum pump. Now dry *n*-pentane (25 ml) was added followed by 1.6 ml (26 mmol) of 2-aminoethanol. Immediately the ethanolamine derivative of 9-BBN began to precipitate out. The mixture was centrifuged and the clean pentane layer was separated. The precipitate was washed with 2 × 20 ml of *n*-pentane, centrifuged, and added to the main fraction. Pentane was distilled off and the residue on vacuum distillation yielded 1.93 g (78%) of cyclohexanol as a colorless liquid, $n^{20}D$ 1.4650, >99% pure by GLC.

B. Sterically Hindered Ketones. Reduction of camphor to borneol and isoborneol is representative of the general procedure utilized.

A typical reaction setup was assembled. Then 3.8 g (25 mmol) of camphor was weighed into it. Now 41.3 ml (26 mmol) of 9-BBN solution in THF was introduced and the contents of the flask were brought to gentle reflux (65 °C). The mixture was stirred for 1 h at that temperature. Then the mixture was cooled to room temperature and the excess 9-BBN destroyed with 0.5 ml of methanol. The reaction

mixture was worked up as in the previous experiment by ethanolamine procedure. Stripping off solvent gave a white solid, which on sublimation gave 3.1 g (81%) of borneols. GLC analysis on a 5% Carbowax 20M column, 6 ft × 0.125 in., indicated 46% isoborneol and 54% borneol.

C. Quinone. The following procedure for the reduction of anthraquinone to 9,10-dihydro-9,10-anthracenediol is representative. A 100-ml flask with a side arm fitted with a Teflon stopcock and a magnetic stirring bar, connected to a mercury bubbler, was flame dried and cooled down to room temperature under dry nitrogen. Then 2.08 g (10 mmol) of anthraquinone was weighed into it. Now 34.1 ml (20 mmol) of 0.586 M 9-BBN solution in THF was added dropwise over a period of 10 min and the resulting mixture stirred well. After 24 h, 0.5 ml of methanol was added, followed by 3.3 ml of 6 N NaOH. THF and volatile solvents were removed under vacuum. The precipitate was filtered and washed each three times with water and cold benzene. There was obtained 1.67 g (79%) of 9,10-dihydro-9,10-anthracenediol as a white solid. A portion was recrystallized from hot benzene: mp 165–175 °C; NMR[25] (Me_2SO-d_6, Me_4Si) δ 5.3 and 5.44 (s, 2, >CH), 6.18 and 6.34 (s, 2, –OH), 7.2–7.9 (m, 8, aromatic).

A small quantity of the diol was converted to the corresponding diacetate by the pyridine–acetic anhydride method: 0.46 g (94%) of colorless needles, mp 171–172 °C, NMR ($CDCl_3$, Me_4Si) δ 2.1 (s, 6, O–CCH_3), 6.97 (s, 2, >CH), 7.2–7.9 (8, aromatic).

D. Carboxylic Acid. The following reduction of *n*-octanoic acid to *n*-octyl alcohol is representative. A 500-ml flask with a side arm fitted with a Teflon stopcock, a magnetic stirring bar, and a reflux condenser connected to a mercury bubbler was flame dried and cooled under a dry stream of nitrogen. Then 158 ml (100 mmol) of a 0.634 M solution of 9-BBN in THF was introduced into the reaction flask. Then 4.05 ml (25 mmol) of *n*-octanoic acid was injected and there was evolved 25.2 mmol of hydrogen. The resulting mixture was brought to careful reflux and stirred at that temperature for 18 h. Then it was cooled to room temperature and excess hydride destroyed with 2 ml of methanol. The boronic acid derivative was oxidized by the addition of 35 ml (105 mmol) of 3 N aqueous sodium hydroxide followed by 25 ml (225 mmol) of 30% hydrogen peroxide at 0 °C and stirring the resulting mixture at 50 °C for 1 h. The aqueous phase was saturated with anhydrous potassium carbonate. The THF layer was separated and the aqueous layer was extracted once with 20 ml of THF and twice with 20-ml portions of ether. The combined organic phase was dried over magnesium sulfate. Distillation of the solvents gave a viscous liquid which on vacuum distillation yielded 2.71 g (83%) of *n*-octyl alcohol, as a colorless liquid, bp 95–97 °C (18 mm), $n^{20}D$ 1.4320.

cis-1,5-Cyclooctanediol, the oxidized product from the 9-BBN moiety, remains as the high-boiling residue in the pot.

E. Acid Chloride. The following procedure for the reduction of hexanoyl chloride to n-hexyl alcohol illustrates the practicality of utilizing 9-BBN for such transformations. An oven-dried 300-ml flask with a side arm and magnetic stirring bar and connected to a mercury bubbler was cooled down to room temperature under a dry stream of nitrogen. The flask was immersed in a water bath (ca. 25 °C) and 94 ml (55 mmol) of a 0.59 M solution of 9-BBN in THF injected into it. This was followed by the addition of 3.55 ml (25 mmol) of distilled hexanoyl chloride. The resulting mixture was stirred for 18 h at 25 °C. Then excess hydride was destroyed with 0.5 ml of methanol. THF was removed under water aspirator and finally over the vacuum pump, and replaced with 25 ml of dry *n*-pentane. Now 3.4 ml (55 mmol) of 2-aminoethanol was added. The ethanolamine derivative of 9-BBN precipitates down. The mixture was centrifuged and the clear pentane layer was separated. The precipitate was washed with 3 × 25 ml of *n*-pentane, centrifuged, and added to the main fraction. Pentane was removed and the residue distilled yielding 2.07 g (81%) of n-hexyl alcohol as a colorless liquid, bp 80 °C (62 mm), $n^{20}D$ 1.4195, >98% pure by GLC.

F. Ester. Reduction of methyl heptanoate to *n*-heptyl alcohol is representative. A typical reaction setup was assembled. Then 101 ml (55 mmol) of 9-BBN solution in THF was introduced into the reaction flask and the flask was carefully brought to reflux temperature. Now 4.2 ml (25 mmol) of methyl heptanoate was added to the reaction mixture and stirred well. After 4 h, the mixture was cooled down to room temperature. Then the reaction mixture was worked up as described in the reduction of hexanoyl chloride. Stripping off the solvent and vacuum distillation of the residue gave 2.23 g (77%) of *n*-heptyl alcohol as a colorless liquid, bp 100 °C (40 mm), $n^{20}D$ 1.4270.

Registry No.—2-Cyclohexen-1-one, 930-68-7; cyclopentanone, 120-92-3; cyclopentene, 142-29-0; methyl heptanoate, 106-73-0; 2-hexyl acetate, 5953-49-1; octanoic acid, 124-07-2; 9,10-dihydro-9,10-antracenediol, 58343-58-1; 9,10-dihydro-9,10-anthracenediol diacetate, 6938-79-0; octyl alcohol, 111-87-5; heptyl alcohol, 111-70-6.

References and Notes

(1) Presented at the 8th Great Lakes Regional Meeting of the American Chemical Society, West Lafayette, Ind., June 1974.
(2) (a) Postdoctoral Research Associate on Grant DA-ARO-D-31-124-73-G148, supported by the U.S. Army Research Office (Durham); (b) Postdoctoral Research Associate on Grant DA-31-124-ARO(D)-453, supported by the U.S. Army Research Office (Durham), and a grant provided by the American Cyanamid Co.
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(6) (a) H. C. Brown, P. Heim and N. M. Yoon, *J. Am. Chem. Soc.*, **92**, 1637 (1970); (b) H. C. Brown, D. B. Bigley, S. K. Arora, and N. M. Yoon, *ibid.*, **92**, 7161 (1970); (c) H. C. Brown, P. Heim, and N. M. Yoon, *J. Org. Chem.*, **37**, 2942 (1972).
(7) 9-BBN is now available commercially from the Aldrich Chemical Co., Milwaukee, Wis., both as the solid and the solution in tetrahydrofuran.
(8) 9-BBN is soluble only to the extent of 0.67 M in THF at 25 °C. Consequently, instead of our usual standard conditions (1.0 M in hydride, 0.25 M in compound, THF, 0 °C) we utilized the present conditions indicated.
(9) It is convenient to discuss the utilization of the reagents in terms of moles of hydride taken up per mole of the compound. However, it should not be confused that free "hydride" ion is the active species. An "active hydride" refers to one B–H bond, 1 equiv of 9-BBN.
(10) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **78**, 5694 (1956).
(11) This convenient precipitation of 9-BBN moiety was developed by Gary W. Kramer of our laboratory for a related application.
(12) It was thought that the high solubility of this adduct in THF may be due to the presence of primary amino group. However, even the complex derived from *N,N*-dimethylethanolamine was found to be highly soluble.
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(22) One molar solution of borane in tetrahydrofuran is now commercially available from Aldrich Chemical Co., Milwaukee, Wis.
(23) For a detailed review of techniques for the handling of air-sensitive substances, see H. C. Brown, G. W. Kramer, A. B. Levy, and M. M. Midland, "Organic Syntheses *via* Boranes", Wiley, New York, N.Y., 1975, pp 191–261.
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Structural Effects in Solvolytic Reactions. 16. The Effect of Conformation of the Cyclopropyl, Phenyl, and Isopropyl Substituents on Their Electronic Contributions to the Electron-Deficient Center

Herbert C. Brown* and James D. Cleveland[1]

Richard B. Wetherill Research Laboratory, Purdue University, West Lafayette, Indiana 47907

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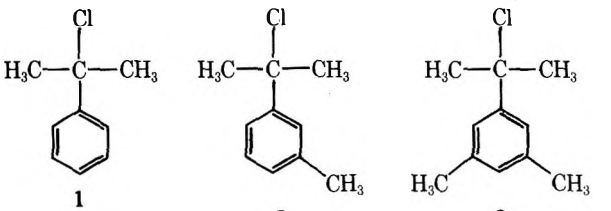
The effect of conformation on the electronic contribution of the cyclopropyl, phenyl, and isopropyl substituents to an electron-deficient center was examined by placing these substituents in the para position of the *tert*-cumyl chloride molecule and determining the rates of solvolysis of these *tert*-cumyl chlorides with no, one, and two *m*-methyl groups flanking the para substituent. The results reveal that there is only a small influence of conformation on the electronic contribution of the isopropyl substituent to the electron-deficient center. On the other hand, there are significant effects of the flanking *m*-methyl groups on the electronic contributions of the cyclopropyl and phenyl substituents to the electron-deficient center. An examination of molecular models indicates that the two flanking *m*-methyl groups compel rotation of the phenyl substituent from the coplanar arrangement of the two aromatic rings believed to favor maximum electronic supply. On the other hand, these models indicate that the two flanking *m*-methyl groups allow, indeed, force the cyclopropyl substituent to assume a quasi-coplanar arrangement with the electron-deficient center. It is therefore concluded that in contrast to the phenyl substituent, such a conformation is not conducive to favorable electronic supply. Therefore, the bisected conformation of the cyclopropyl substituent, which is possible both in the monomethyl and unmethylated derivatives, strongly facilitates electronic contributions to the electron-deficient center.

The effect of conformation on the maximum orbital overlap of a group with an adjacent p orbital has been the subject of numerous investigations over the years by experimental and theoretical chemists.[2] In particular, the effects of conformation of phenyl,[2c-e,3] cyclopropyl,[4] and alkyl[2a,b,4g,5] groups on the stability of adjacent carbonium ions have been extensively studied.

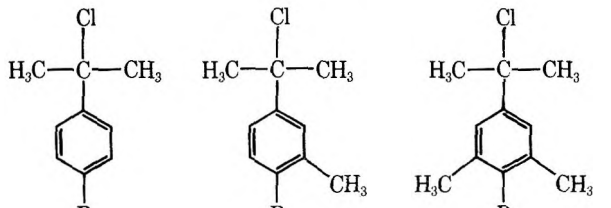
We have measured the effect of conformation on the electronic contributions of cyclopropyl, phenyl, and isopropyl substituents to the electron-deficient center of the developing *tert*-cumyl cation. This examination required the synthesis and measurement of the rate of solvolysis of the series of compounds **1–6.** In compounds **4–6,** solvolysis affords a carbonium ion of which a resonance structure places a positive charge in the para position where the group R may satisfy the electron deficiency generated (eq 1).

Inasmuch as no resonance interactions are possible in the meta positions, the inductive contributions of the *m*-methyl groups are constant throughout the series **2, 3, 5,** and **6.** However, the rate of a para-substituted *tert*-cumyl chloride relative to unsubstituted *tert*-cumyl chloride (**1**) measures both the inductive and conjugative (either resonance or hyperconjugation) contribution of a given substituent. Evidence is available which demonstrates that the inductive effect of a group is nearly the same in the meta and para positions of benzene derivatives.[6] Thus any difference in rate of a para- vs. a meta-substituted *tert*-cumyl chloride relative to **1** is a measure of the additional conjugative contributions of a given substituent.

Each of the substituents (cyclopropyl, phenyl, and isopropyl) whose total electronic contribution is measured in **4a–c,** is forced into a definite conformation with respect to the electron-deficient center in the series **5a–c** and **6a–c.** The inductive effects of the *m*-methyl groups are small and are taken to be additive throughout the series **2, 3, 5,** and **6.** It is usually found that the combined effect of two substituents can be represented by the product of their individual rates relative to the unsubstituted parent compound. Indeed, data are available for many reactions to confirm this additivity relationship.[7-13] Thus the additivity relationship predicts that the rates of the series **5a–c** and **6a–c** will be equal to the product of the rates of the individual substituents relative to

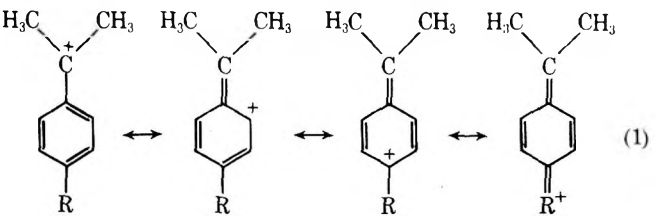


1 **2** **3**



4 **5** **6**

a, R = phenyl
b, R = isopropyl
c, R = cyclopropyl



(1)

tert-cumyl chloride. The difference between predicted and observed rates in the series **5a–c** and **6a–c** measures the effect of conformation on the electronic contribution of each of the three substituents in carbonium ion reactions.

Special interest is centered in the series **4c–6c,** where solvolysis affords carbonium ions, resonance structures of which give species analogous to cyclopropylcarbinyl cations. Cyclopropylcarbinyl cations exhibit special behavior. To account for such behavior, several theoretical models with definite conformational requirements for their existence have been proposed. The conformational limitations imposed upon the cyclopropyl substituent in **5c** and **6c**[4k] permit a choice to be made among the various proposed theoretical models by

Table I. Rate Constants and Derived Data for the Solvolysis of *tert*-Cumyl Chlorides in 90% Aqueous Acetone

Registry no.	Substituents	k_1, $s^{-1} \times 10^5$ 0.0 °C	k_1, $s^{-1} \times 10^5$ 25.0 °C	R k_1/k_H (25 °C)	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta F^{\ddagger} - \Delta F_0^{\ddagger}$
934-53-2	None	0.60	12.4	1.0	19.0	−12.6	0
13240-60-3	3-Methyl[a]	1.26	24.8	2.0	18.6	−11.8	−0.41
10477-70-0	3,5-Dimethyl[b]	2.44	47.3	3.9	18.6	−11.3	−0.81
42325-37-1	4-Phenyl	4.89	94.8	7.65	18.6	−9.9	−1.20
58502-71-9	3-Methyl-4-phenyl	3.17	61.7	4.98	18.6	−10.7	−0.95
58502-72-0	3,5-Dimethyl-4-phenyl	3.91	74.9	6.04	18.5	−10.6	−1.07
5650-08-8	4-Isopropyl	13.6	223	18.0	17.5	−11.8	−1.71
58502-73-1	3-Methyl-4-isopropyl	22.4	341[c]	27.5	17.0	−12.6	−1.96
58502-74-2	3,5-Dimethyl-4-isopropyl	34.5	507[c]	40.9	16.8	−12.6	−2.20
7175-64-6	4-Cyclopropyl	146.5	1905[c]	154	16.0	−12.6	−2.98
10477-69-7	3-Methyl-4-cyclopropyl	162.7	2100[c]	169	16.0	−12.6	−3.04
10477-71-1	3,5-Dimethyl-4-cyclopropyl	30.3	447[c]	36.0	16.9	−12.7	−2.12
40349-51-7	3,4-Dimethyl[c]	42.6	634	51.1	16.0	−14.8	−2.33
7243-79-0	4-Methyl[a]	20.6	322	26.0	17.3	−12.0	−1.92
19936-08-4	3-Isopropyl[a]	1.05	23.2	1.87	19.4	−10.2	−0.37
58502-75-3	3-Phenyl[d]		3.97	0.32	19.3	−13.9	0.67
19936-06-2	3-Cyclopropyl[e]	0.89	19.0	1.53	19.3	−10.9	−0.25

[a] Reference 17. [b] Unpublished research with T. Inukai. [c] Calculated from data at lower temperatures. [d] Reference 16. [e] Reference 53.

Table II. Rate Constants and Derived Data for the Solvolysis of *tert*-Cumyl Chlorides in 97.5% Aqueous Acetone

Substituents	k_1, $s^{-1} \times 10^5$ 0.0 °C	k_1, $s^{-1} \times 10^5$ 25.0 °C	R k_1/k_H (25 °C)	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta F^{\ddagger} - \Delta F_0^{\ddagger}$
None	0.023[a]	0.46	1.0	18.8	−19.8	0
4-Isopropyl	0.46	7.15	15.5	17.2	−19.8	−1.63
3-Methyl-4-isopropyl	0.71	11.7	25.4	17.6	−17.6	−1.92
3,5-Dimethyl-4-isopropyl	1.26	18.8	40.9	16.9	−18.8	−2.20
4-Cyclopropyl	3.02	40.1	87.2	16.2	−19.8	−2.65
3-Methyl-4-cyclopropyl	3.41	44.5	96.7	16.1	−20.0	−2.71
3,5-Dimethyl-4-cyclopropyl	0.93	15.3	33.2	17.6	−17.1	−2.12

[a] Calculated from data at other temperatures.

Table III. Relative Rates of Solvolysis of Substituted *tert*-Cumyl Chlorides in 90% Aqueous Acetone at 25.0 °C

Substituted *tert*-cumyl chloride	k_{rel}	Effect of para substituent	% electronic contribution maintained
Hydrogen	1.0		
3-Methyl	2.0		
3,5-Dimethyl	3.9		
4-Phenyl	7.7	7.7	100
3-Methyl-4-phenyl	5.0	2.5	32.5
3,5-Dimethyl-4-phenyl	6.0	1.6	20.2
4-Isopropyl	18.0	18.0	100
3-Methyl-4-isopropyl	27.5	13.8	76.4
3,5-Dimethyl-4-isopropyl	40.9	10.5	58.3
4-Cyclopropyl	154	154	100
3-Methyl-4-cyclopropyl	169	84.5	54.9
3,5-Dimethyl-4-cyclopropyl	36.0	9.2	5.8
4-Methyl	26.0	26.0	100
3,4-Dimethyl	51.1	25.6	98.3
2-Fluorenyl	173	43.3	

comparison of predicted and observed rates in the series **4c–6c**. The isopropyl series **4b–6b** provides a steric and electronic approximation of the cyclopropyl series as well as providing information about the conformational requirements of the isopropyl substituent itself. The phenyl substituent, known to have conformational requirements from earlier studies of biphenyl compounds,[14,15] provides a reference against which the conformational requirements of the isopropyl and cyclopropyl substituents can be compared.

Results and Discussion

The appropriate kinetic data are summarized in Tables I–III. Because of the difficulty in following the rapid rates of some of the substituted *tert*-cumyl chlorides at 25 °C in 90% aqueous acetone by the titrimetric method used in previous rate studies of substituted *tert*-cumyl chlorides,[16,17] the rates of solvolysis of these compounds were calculated from data at other temperatures. As a check on the rates thus calculated, the rates of solvolysis of these compounds were also measured at 0 and 25 °C in 97.5% aqueous acetone. An excellent correlation between the two solvents was observed. With the exception of compounds **4c** and **5c**, both of which exhibited special rate enhancements, an approximately 30-fold decrease was observed in determining a given compound in 97.5% vs. 90% aqueous acetone. Earlier studies had shown that values of k_1/k_H do not change significantly in aqueous acetone of varying composition[18] and that entropy terms for a series of closely related compounds do not exhibit major variations.[19] An excellent parallel relationship of k_1/k_H between the two solvents of varied acetone content and agreement of entropy values within a given solvent system were observed.

The desired *tert*-cumyl chlorides were synthesized by treating the substituted phenyldimethylcarbinol or the corresponding olefins dissolved in methylene chloride with hydrogen chloride at 0 °C using the automatic hydrochlorinator apparatus.[20] Inasmuch as the tertiary chlorides are unstable and difficult to purify, we were content to prepare pure sam-

ples of the tertiary alcohols or olefins, and to use the crude tertiary chlorides directly without further treatment. It has been demonstrated previously that this procedure has no measurable effect on the measured rate of solvolysis.[17]

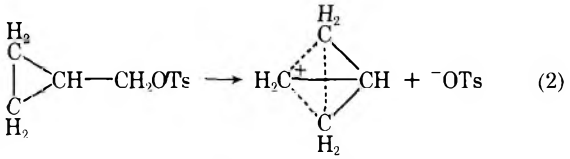
Perusal of the kinetic data for each of the meta- and para-substituted *tert*-cumyl chlorides indicated a rate enhancement for each of the substituents in the para position relative to 1. The para/meta relative rates in 90% aqueous acetone for each of the substituents are cyclopropyl, 101; phenyl, 23.4; isopropyl, 9.53. Thus the enhancement in rates cannot be due to inductive effects and must be due to special conjugative interactions which are possible in the para position, but not in the meta position.

Conformational Requirements of the Cyclopropyl Substituent. The *p*-cyclopropyl substituent produced the greatest enhancement in rate and exhibited the most pronounced effect of conformation upon electronic contribution to the electron-deficient center of any of the substituents studied in this investigation.

Considerable interest has surrounded the carbonium ion type reactions of cyclopropylcarbinyl derivatives. A vast body of literature exists which establishes the unusual ability of a cyclopropyl substituent to interact conjugatively with an adjacent electron-deficient center.[4,21] Cyclopropylcarbinyl cations are remarkably stable. Solvolyses leading to the formation of such ions exhibit dramatically enhanced rates. An example of this behavior is offered by the solvolysis of tertiary 2-R-2-propyl *p*-nitrobenzoates.[22] Thus major increases are exhibited from the 2-methyl derivative (1.0) to 2-phenyl (969) to cyclopropyl (503 000).

Many structures for the cyclopropylcarbinyl cation have been considered. Indeed, to account for the ease of interconversion of cyclopropylcarbinyl, cyclobutyl, and allylcarbinyl derivatives and the markedly enhanced solvolytic rates of cyclopropylcarbinyl derivatives, several different intermediate ions have been proposed in the literature. For example, tricyclobutonium,[23] unsymmetrical bicyclobutonium,[24] delocalized cyclobutyl[25] (symmetrical bicyclobutonium), bisected cyclopropylcarbinyl[4d] (symmetrical), and unsymmetrical homoallylic ions[26] have been advanced.

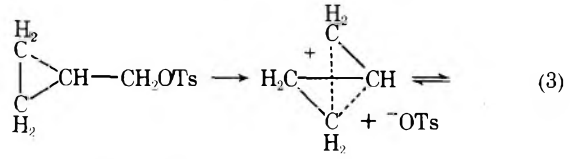
The fast rate of solvolysis of cyclopropylcarbinyl tosylate was originally attributed to the stabilization of the transition state leading to the formation of the presumably highly stabilized symmetrical tricyclobutonium ion (eq 2). This species



(2)

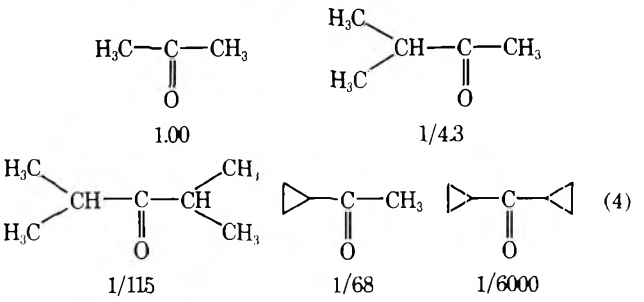
is σ bridged. Note that it contains three carbon atoms bonded to five different atoms.

Later it was observed that the reactions of tagged cyclopropylcarbinyl derivatives did not show the full equilibration of the tag required by the tricyclobutonium ion.[27] Consequently, it was proposed that the cyclopropylcarbinyl cation exists as a rapidly equilibrating set of three equivalent bicyclobutonium ions (eq 3). This is a σ-bridged species with one carbon atom bonded to five nearest neighbors.



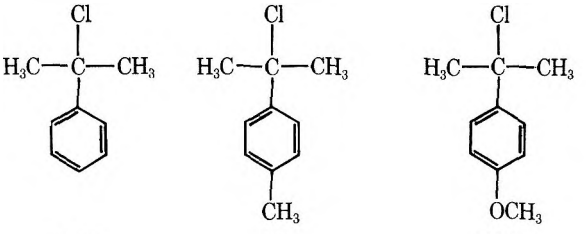
(3)

It was shown by Hart and Sandri that a number of secondary and tertiary derivatives containing cyclopropyl groups undergo solvolysis with similar rate enhancements but without rearrangements.[28] Consequently, the cyclopropyl group is capable of providing electron density to stabilize a carbonium ion without rearrangement of the structure occurring. Similarly, a study of the rates of reduction of ketones containing cyclopropyl groups established that these rates are quite low[29] (4). Consequently, the cyclopropyl group is capable of providing electron density to the carbonyl group in these ketones, as well as to the electron-deficient centers of carbonium ion.



1.00 1/4.3 1/115 1/68 1/6000 (4)

The standard tool of the organic chemist in exploring electron deficiency in an organic system is to introduce substituents into the appropriate positions and ascertain the effect. For example, the proposed explanation for the stabilizing effect of the phenyl group in stabilizing the *tert*-cumyl cation postulates delocalization of the positive charge from the carbonium carbon to the ortho and para positions of the aromatic ring (1). Introduction of methyl and methoxy substituents into the para position of the *tert*-cumyl system should assist in satisfying this electron deficiency and result in an increase in the stability of the cation and an increase in the rate of solvolysis. This is observed[2d] (5).



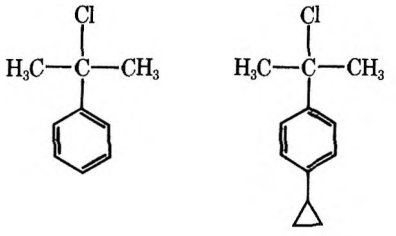
1.00 26 3360 (5)

If the cyclopropyl group stabilizes a carbonium ion center to which it is attached, it should develop an electron deficiency in the ring.[4k] Indeed, the introduction of a methyl group or an ethoxy group into the ring results in large rate enhancements.[30] Moreover, these rates give a linear plot against the σ^+ constants.

Moreover, the authors made a detailed study of the effect of cumulative methyl groups.[30] They noted an unusually good additivity for each successive methyl substituent. The introduction of a 2- or 3-methyl substituent has almost the same effect [the factor for a trans 2- or 3-methyl (10–11) is slightly larger than the cis factor (7–10)] regardless as to whether or not there was already one such substituent. On the assumption that the ions have similar structures in the transition states leading to them, it was concluded that electron supply from the cyclopropyl ring must involve a symmetrical contribution and that their results are not consistent with the bicyclobutonium ion formulations.

We explored the electronic contributions of the cyclopropyl substituent in the para position of the *tert*-cumyl system.[31] We also came to the conclusion that the electronic contributions from the cyclopropyl substituent cannot involve σ bridging through space.

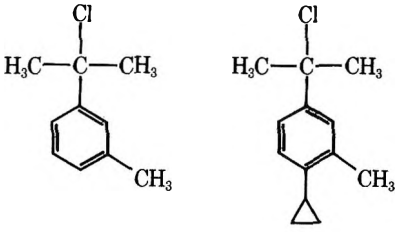
A *p*-isopropyl group increases the rate of solvolysis of *tert*-cumyl chloride in 90% aqueous acetone at 25 °C by a factor of 18. On the other hand, a *p*-cyclopropyl group is much more effective—it increases the rate by a factor of 154 (6). A



(6)

rel rate 1.0 154

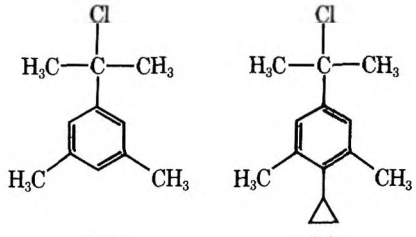
single *o*-methyl substituent, as in 3-methyl-4-cyclopropyl-*tert*-cumyl chloride, increases the relative rate to 169. Correcting for the contribution of the *m*-methyl substituent, a factor of 2, reveals only a modest decrease in the effect of the cyclopropyl group accompanying the introduction of the single methyl substituent (7). On the other hand, the observed rel-



(7)

rel rate 1.0 84.5

ative rate for 3,5-dimethyl-4-cyclopropyl-*tert*-cumyl chloride is 36. Correcting this for the contribution of two *m*-methyl substituents, a factor of 4, reveals a sharp drop in the contribution of the cyclopropyl substituent to the rate, to a factor of only 9 (8). Thus, with two o-methyl substituents, the con-



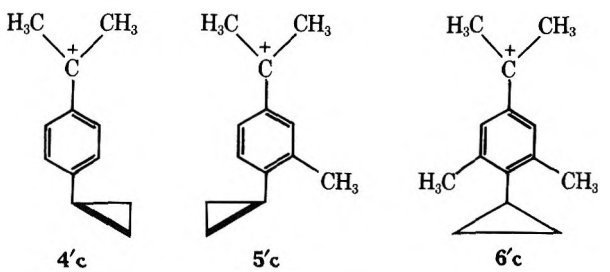
(8)

rel rate 1.0 9.0

tribution of the *p*-cyclopropyl substituent to the rate drops from its original high value of 154 down to a low value of 9, even lower than the effect of a simple alkyl substituent, such as 18 for isopropyl.

Parallel k_R/k_H values for the cyclopropyl substituted compounds were observed in both 90 and 97.5% aqueous acetone.

There is increasing evidence that the maximum interaction between a cyclopropane group and an adjacent electron-deficient center is achieved with the bisected conformation.[4,21a,b,30,32-34] Such a bisected arrangement for the cyclopropyl substituent in the *tert*-cumyl system readily accounts for the pronounced effect of the conformation of the cyclopropyl group on the relative rates. This is apparent from the examination of the structures **4'c–6'c.** The bisected arrange-



4'c **5'c** **6'c**

ment of the cyclopropyl group, shown in **4'c,** would not be seriously affected by the introduction of a single methyl group, as shown in **5'c.** However, two methyl substituents effectively block this conformation **5'c,** greatly reducing the electronic contributions from the cyclopropyl substituents.[4k]

Indeed, from a study of the reactivity of geometrically constrained cyclopropylcarbinyl systems as a function of angle, the reactivity (ranging over 11 powers of ten) of cyclopropylcarbinyl cations was shown to be a continuous function of the geometry between the vacant p orbital and the cyclopropyl ring.[35] The authors further noted that the cyclopropylcarbinyl cation with 60° geometry, approximately the geometry of a bicyclobutonium ion, is considerably less stable than the ion with 30 or 0° (i.e., bisected) geometries.[35] Moreover, solvolyses of optically active cyclopropylmethylcarbinyl derivatives do not yield optically active products.[36] A σ-bridged intermediate would have been expected to retain asymmetry.

Clearly, the enhanced rate of solvolysis of cyclopropylcarbinyl derivatives is not the result of σ bridging through space of the carbonium ion center with one or both of the more distant carbon atoms of the ring.

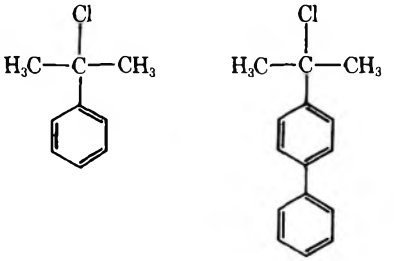
Although beyond the scope of the present publication, it should be pointed out that a σ-bridged structure has been proposed for the primary cyclopropylcarbinyl cation under stable ion conditions.[4a] This conclusion was based on a discrepancy between the observed ^{13}C shift and that calculated for a set of equilibrating classical cations. However, recent test of another NMR criterion proposed for such a σ-bridged cation, a high $J_{^{13}C-H}$ coupling constant for the methine hydrogen, has given negative results.[4l] Consequently, the original conclusion[4a] must be considered questionable.[4l]

Conformational Requirements of the Phenyl Substituent. Resonance between the developing p orbital of a cationic center and the π system of an aryl ring plays an important part in facilitating solvolysis of benzyl systems.[2c-e,3,37] For an aryl group to exhibit its maximum electronic contribution via resonance, it must assume a coplanar arrangement with the electron-deficient center.

The conformational requirements of a phenyl group are examined in the *p*-phenyl-*tert*-cumyl system.

Biphenyl exists in the gas phase in a noncoplanar conformation with an angle of approximately 45° between the plane of the two rings.[38,39] The electronic spectrum of biphenyl indicated an interplanar angle of 20° in solution and 40–43° in the vapor state.[40] The molecule presumably assumes this twisted conformation to minimize the steric interactions of the four ortho hydrogens. However, the relief of these steric interactions should also reduce the resonance contributions of a *p*-phenyl substituent in the solvolysis of *p*-phenyl-*tert*-cumyl chloride.

A *p*-phenyl group increases the rate by a factor of 7.65 (9).



(9)

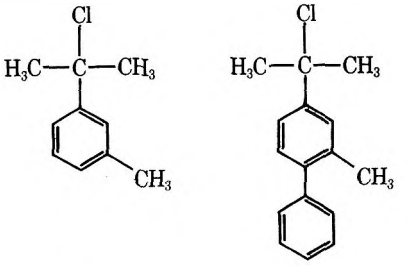
rel rate 1.00 7.65

Indeed, this is much lower than the rate increase of 43 for a *p*-phenyl group when corrected for the noncoplanarity.[14]

Since the interplanar angle of the rings in biphenyl is 20° in solution, this would account for the observed behavior of a phenyl group being a poorer source of electron density than an alkyl group in the *tert*-cumyl system. The $-I$ effect of the phenyl group would continue to be operative in the para po-

sition while the +*R* effect would be diminished owing to the deviation from coplanarity of the rings.

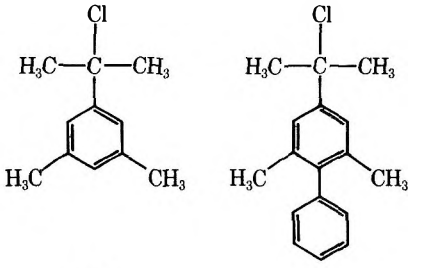
The introduction of an *o*-methyl group into biphenyl is reported to increase the interplanar angle in solution of *o*-methylbiphenyl to about 60°.[40] Hence there is less orbital overlap between the phenyl rings than in biphenyl. Indeed, this is exemplified in the decrease in the effect of a *p*-phenyl group by the introduction of a methyl group ortho to the *p*-phenyl group (10).



(10)

rel rate 1.00 2.49

The substitution of a second methyl group ortho to the *p*-phenyl substituent produces an additional loss of the electronic contribution of the phenyl substituent (11). Thus there must be substantial deviation from coplanarity of the rings.



(11)

rel rate 1.00 1.55

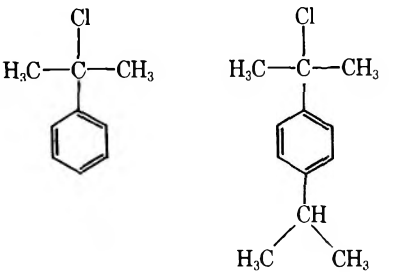
Thus the observed conformational requirements on the electronic contributions of the phenyl group are consistent with other reports. For example, a rate decrease resulting from steric inhibition to resonance was demonstrated by the introduction of ortho substituents into the *tert*-cumyl system.[42] In the solvolysis of 1-naphthyl-2-propyl chloride, the peri hydrogen is reported to interfere sterically with the preferred coplanar arrangement.[43]

Moreover, in a study of the solvolysis of highly crowded aryldialkylcarbinyl *p*-nitrobenzoates, it was shown that as the molecule becomes more crowded around the cationic center, the cation is less able to assume the planar conformation.[44] Hence the aryl group will be twisted out of coplanarity. This results in a marked decrease in reactivity.

Conformational Requirements of the Isopropyl Substituent. In a number of reactions of alkylated benzene derivatives an electron release from the alkyl groups in the order of methyl > ethyl > isopropyl > *tert*-butyl is observed (the Baker–Nathan order),[45] a sequence opposite to that of the usual inductive effect order, methyl < ethyl < isopropyl < *tert*-butyl. The Baker–Nathan order has been attributed to hyperconjugation[5a,46-49] in which carbon–hydrogen hyperconjugation is more effective than carbon–carbon hyperconjugation.

The conformational requirements of an isopropyl group were examined in the para position of the *tert*-cumyl system. The isopropyl substituent exhibited the smallest effect of conformation on electronic contribution to an electron-deficient center of any of the three substituents studied.

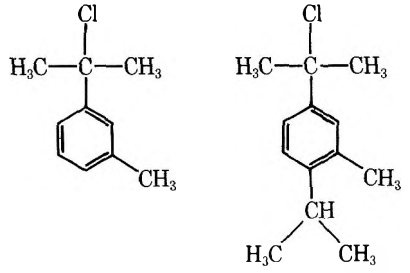
A *p*-isopropyl substituent in *tert*-cumyl chloride increases the rate by a factor of 18.0 (12).



(12)

rel rate 1.0 18.0

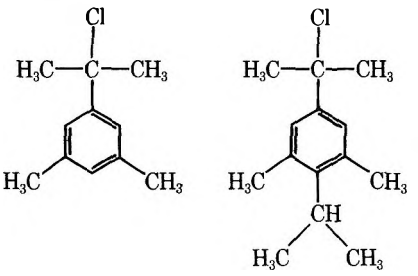
With a methyl group ortho to the isopropyl group, the stabilizing influence of the *p*-isopropyl on the rate decreases to 13.8 (13).



(13)

rel rate 1.0 13.8

Two methyl groups ortho to the isopropyl group resulted in a further decrease in the electronic contributions of the *p*-isopropyl. Thus the effect of the *p*-isopropyl substituent on the rate is only 10.5 (14). Parallel k_R/k_H values for the



(14)

rel rate 1.0 10.5

isopropyl substituted compounds were observed in both 90 and 97.5% aqueous acetone.

These results are suggestive of an example of steric inhibition of hyperconjugation. Possible steric interactions which are absent in 4-isopropyl-*tert*-cumyl chloride become more important in 3-methyl-4-isopropyl-*tert*-cumyl chloride and especially prominent in 3,5-dimethyl-4-isopropyl-*tert*-cumyl chloride. These increasing steric interactions would place the isopropyl group in a conformation in which the more important carbon–hydrogen hyperconjugation would be less likely. Hence, there is a decrease in the effectiveness of the *p*-isopropyl in stabilizing the transition state during ionization.

In a study of the relationship between hyperconjugation and conformation analogous to this investigation, the ethanolysis of 4-alkyldiphenylmethyl (4-alkylbenzhydryl) chlorides, where the alkyl group was methyl, ethyl, *n*-propyl, isobutyl, and neopentyl, exhibited rates decreasing in the order cited.[50] Thus the rate diminishes progressively as the nonbonding interaction of the side chain and the aromatic ring hinder carbon–hydrogen hyperconjugation. They also studied the corresponding 3,5-dimethyl-4-alkyldiphenylmethyl chlorides where the alkyl group was methyl, ethyl, and *n*-propyl. Here the investigators concluded that the hyperconjugative effect of a primary alkyl group is not affected by torsional rotation of the group about the bond between it and the benzene ring.[50]

It might be suggested that in the *p*-isopropyl-*tert*-cumyl system the results could also be explained by the increasing

steric hindrance to solvation of the para position as methyl groups are substituted in the 3 and 5 positions.[51] However, the observed rate of 3,4-dimethyl-*tert*-cumyl chloride coincides with the rate predicted by the additivity principle. Thus, the full electronic contribution of the 4-methyl substituent is maintained in contrast to the diminished electronic contribution of the 4-isopropyl substituent.

Experimental Section

All products yielded physical constants in agreement with literature values and/or microanalytical data within the accepted limits as well as NMR spectra in agreement with the indicated structures. All spectra were run at 60 MHz and chemical shifts are expressed as δ values relative to internal tetramethylsilane. Homogeneity of the products was established by gas chromatographic examination.

The precursors to the 4-substituted *tert*-cumyl chlorides, *p*-isopropylphenyldimethylcarbinol,[17] 4-diphenyldimethylcarbinol,[52] and *p*-cyclopropyl-α-methylstyrene[53] were prepared by previously reported methods.

Preparation of Precursors to the Methyl-Substituted 4-Phenyl-*tert*-cumyl Chlorides. 3-Methyl-4-phenyl-α-methylstyrene. 3-Methyl-4-phenylbromobenzene[54] [bp 120–122 °C (1.5 mm), n^{20}D 1.6209] was converted into a Grignard reagent and allowed to react with acetone, and distillation of the crude product gave a 46.3% yield of the olefin, bp 120–122 °C (1.5 mm), n^{20}D 1.5994. The ^{1}H NMR spectrum showed peaks at δ 2.22 (s, 3 H, 3-methyl), 2.10 (m, 3 H, α-methyl), 4.97 and 5.28 (m, 2 H, olefinic protons), and 7.05–7.30 (m, 3 H, aromatic).

Anal. Calcd for $C_{16}H_{16}$: C, 92.26; H, 7.74. Found: C, 92.16; H, 7.99.

Gomberg Reaction between 5-Isopropyl-*m*-xylene and Aniline. Following procedures suggested by Hey[55] and Gomberg and Pernert[54] for analogous compounds, aniline was diazotized and allowed to react with 5-isopropyl-*m*-xylene to give an 18.4% yield of a 64/36 mixture of **3,5-dimethyl-4-phenylisopropylbenzene** and **3,5-dimethyl-2-phenylisopropylbenzene,** respectively. The 64/36 mixture was fractionated through a Todd column with a rating of 60 plates, operating at a 15:1 reflux ratio to give fractions enriched in the higher boiling 3,5-dimethyl-4-phenylisopropylbenzene and the fractions were separated using preparative vapor phase chromatography (F & M Model 770 automatic preparative gas chromatograph, Carbowax 20M on Chromosorb W, 200–250 °C, temperature programmed, 7.5 °C/min). One fraction from the Todd column fractionation, bp 140 °C (6 mm), analyzed pure by VPC analysis (Perkin-Elmer 226 instrument, 150-ft Apiezon L capillary column, 150 °C) for 3,5-dimethyl-4-phenylisopropylbenzene, n^{20}D 1.5600. The ^{1}H NMR spectrum showed peaks at δ 2.80 (septet, 1 H, methine proton), 1.25 (d, 6 H, isopropyl CH_3's), 1.96 (s, 3- and 5-methyl groups), 6.76 (s, 2 H, 2- and 6-protons), and 6.9–7.32 (m, 5 H, 4-phenyl protons).

Anal. Calcd for $C_{17}H_{20}$: C, 91.01; H, 8.99. Found: C, 90.82; H, 9.05.

A VPC purified sample of 3,5-dimethyl-2-phenylisopropylbenzene gave n^{20}D 1.5604. The ^{1}H NMR spectrum showed peaks at δ 2.63 (septet, 1 H, methine proton), 1.07 (d, 6 H, isopropyl CH_3's), 1.88 (s, 3 H, 3-methyl), 2.28 (s, 3 H, 5-methyl), 6.74 (d, 1 H, 6-proton), 6.84 (d, 1 H, 4-proton), and 6.88–7.32 (m, 5 H, 2-phenyl protons).

3,5-Dimethyl-4-phenylacetophenone. The oxidation was carried out according to eq 15

$$3\text{Ar}—i\text{-}C_3H_7 + 10CrO_3 + 30HOAc \xrightarrow{Ac_2O} 3\text{Ar}—COCH_3 + 3CO_2 + 21H_2O + 10Cr(OAc)_3 \quad (15)$$

found to be general for the selective oxidation of an exposed isopropyl group. In a 100-ml round-bottom flask equipped with a drying tube were placed 3,5-dimethyl-4-phenylisopropylbenzene (6.0 g, 0.0268 mol), acetic acid (16.1 g, 0.268 mol, 15.3 ml), and acetic anhydride (15.3 ml). Chromium trioxide was added portionwise in small amounts so that at no time did the temperature exceed 30–35 °C. A temperature rise accompanied each addition and after the addition was complete, an additional 16 ml of glacial acetic acid was added, and the solution stirred overnight. The mixture was then poured on ice and most of the acetic acid was neutralized, although care was taken to not reach the point where chromium salts would precipitate. Ether was added, the aqueous layer thoroughly extracted, and the combined ether extracts thoroughly washed with 10% sodium hydroxide to remove all acetic acid and then washed with water and dried over sodium sulfate/magnesium sulfate. Removal of solvent yielded 3.04 g (0.0136 mol) of the crude ketone corresponding to a 50.7% yield. A sample purified by preparative VPC (Aerograph instrument, Dow Corning Silicone 550 on Chromosorb W, 200 °C) gave the pure ketone, mp 73.5–74.5 °C, 2,4-DNP 249–250 °C. The ^{1}H NMR spectrum showed peaks at δ 2.04 (s, 6 H, 3- and 5-methyls), 2.48 (s, 3 H, acetyl methyl), 6.87–7.40 (m, 5 H, 4-phenyl protons), and 7.50 (s, 2 H, 2- and 6-aromatic protons).

Anal. Calcd for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 85.89; H, 7.18.

3,5-Dimethyl-4-phenyl-*tert*-cumyl Alcohol. 3,5-Dimethyl-4-phenylacetophenone was heated with methylmagnesium iodide to give an 81.8% yield of the carbinol, mp 120–121 °C (from 60–65 °C petroleum ether). The ^{1}H NMR spectrum showed peaks at δ 1.60 (s, 6 H, dimethylcarbinyl protons), 2.02 (s, 6 H, 3- and 5-methyls), and 6.95–7.39 (m, 7 H, aromatic).

Anal. Calcd for $C_{17}H_{20}O$: C, 84.95; H, 8.39. Found: C, 85.18; H, 8.12.

Preparation of Precursors to the Methyl-Substituted 4-Isopropyl-*tert*-cumyl Chlorides. 2-Chloromethyl-1,4-diisopropylbenzene. The procedure suggested for the chloromethylation of an analogous compound was used.[56] Chloromethylation of 1,4-diisopropylbenzene[57] using stannic chloride and chloromethyl methyl ether gave a 79.8% yield of the desired compound, bp 124 °C (5 mm), n^{20}D 1.5175. The ^{1}H NMR spectrum showed peaks at δ 1.23 (d, 6 H, 4-isopropyl methyls), 1.25 (d, 6 H, 1-isopropyl methyls), 2.83 (septet, 1 H, methine proton of 4-isopropyl group), 3.25 (septet, 1 H, methine proton of 1-isopropyl group), 4.52 (s, 2 H, 2-chloromethyl protons), and 6.98–7.12 (m, 3 H, aromatic).

Anal. Calcd for $C_{13}H_{19}Cl$: C, 74.09; H, 9.09; Cl, 16.82. Found: C, 74.27; H, 9.04; Cl, 16.53.

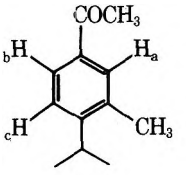
2-Methyl-1,4-diisopropylbenzene. Reduction of 2-chloromethyl-1,4-diisopropylbenzene using lithium aluminum hydride and lithium hydride[58] in tetrahydrofuran gave a 95.5% yield of the hydrocarbon, bp 71 °C (1.2 mm), n^{20}D 1.4977. The ^{1}H NMR spectrum showed peaks at δ 1.19 (d, 12 H, 1,4-diisopropyl methyls), 2.76 (septet, 1 H, methine proton of 1-isopropyl), 3.03 (septet, 1 H, methine proton of 4-isopropyl), 2.25 (s, 3 H, 2-methyl), and 6.74–6.98 (m, 3 H, aromatic).

Anal. Calcd for $C_{13}H_{20}$: C, 88.57; H, 11.73. Found: C, 88.66; H, 11.67.

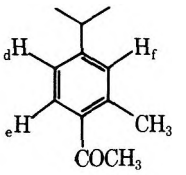
3-Methyl-4-isopropylacetophenone. 2-Methyl-1,4-diisopropylbenzene was oxidized by the chromium trioxide procedure described for 3,5-dimethyl-4-phenylacetophonone to give a 40.1% yield of the ketone, bp 84 °C (0.3 mm), n^{20}D 1.5249 [lit.[59] bp 254–256 °C (740 mm), n^{20}D 1.5320]. Gas chromatographic analysis (Perkin-Elmer 154 instrument, Dow Corning Silicone 550 on Chromosorb W, 155 °C) indicated the product to be homogeneous.

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.75; H, 9.07.

The choice was between two possible ketonic products:



7



8

Structure 7 predicts that two protons will be shifted downfield due to the deshielding effect of the aceto group and one proton would appear upfield. (Both H_a, broad doublet due to meta coupling with H_b, and H_b, AB pattern with meta coupling, would appear downfield while H_c, AB pattern, would appear upfield). Structure 8 predicts the opposite: two protons appearing upfield and one proton appearing downfield (H_d, AB pattern with meta coupling, and H_f, broad doublet due to meta coupling with H_d, both appearing upfield, while H_e, AB pattern, would appear downfield). The spectrum observed is exactly that predicted for 3-methyl-4-isopropylacetophenone (7): H_a, broad doublet due to meta coupling with H_b, δ 7.57; H_b, AB pattern with meta coupling, δ 7.63; and H_c, AB pattern, δ 7.15 (cf. structure 7).

3-Methyl-4-isopropyl-α-methylstyrene. 3-Methyl-4-isopropylacetophenone was treated with methylmagnesium iodide to give a 94.9% yield of the crude carbinol which upon purification by preparative VPC (Aerograph instrument, Dow Corning Silicone 550 on Chromosorb W, 200 °C) gave the dehydration product, the olefin, n^{20}D 1.5322. The ^{1}H NMR spectrum showed peaks at δ 1.22 (d, 6 H, 4-isopropyl methyls), 2.29 (s, 3 H, 3-methyl), 3.08 (septet, 1 H, methine proton of isopropyl), 2.07 (m, 3 H, α-methyl group), 4.91 [m, 1 H, olefinic (cis to α-methyl)], 5.20 [m, 1 H, olefinic (trans to α-methyl)], and 7.09 (s, 3 H, aromatic).

Anal. Calcd for $C_{13}H_{18}$: C, 89.59; H, 10.41. Found: C, 89.50; H, 10.13.

Alkylation of 5-Isopropyl-*m*-xylene. In a 2-l. three-necked flask fitted with a stirrer and thermometer were placed reagent grade 5-isopropyl-*m*-xylene (250 g, 1.69 mol) and isopropyl alcohol (96 g, 1.60

mol). The solution was cooled to 0 °C. Previously cooled (~0 °C) 80% aqueous sulfuric acid (567 ml) was added at a rate such that the temperature did not exceed 20 °C during the addition. After the addition was complete, the reaction mixture was stirred for 3 days at room temperature. VPC analysis of an aliquot (Perkin-Elmer 154, Carbowax 20M on Chromosorb W, 90 °C) indicated approximately 50% conversion of the starting material. The layers were separated, and the organic layer washed with dilute base and then water and dried over sodium sulfate/magnesium sulfate. Removal of the unreacted 5-isopropyl-*m*-xylene, bp 89 °C (19 mm), using a Todd column left 130 g of isopropyl alkylates. VPC analysis (Perkin-Elmer 226, 150-ft, Carbowax 20M capillary column, 90 °C) indicated two major isomers which constituted 98% of the isopropyl alkylates. Utilizing the F & M 770 automatic preparative gas chromatograph (Carbowax 20M on Chromosorb P, 100–190 °C, temperature programmed at 7.5 °C/min) the isomers were separated to give **2,6-dimethyl-1,4-diisopropylbenzene** (55%), n^{20}D 1.5070, and **3,5-dimethyl-1,2-diisopropylbenzene** (45%), n^{20}D 1.5064. The ^{1}H NMR spectrum of 2,6-dimethyl-1,4-diisopropylbenzene showed peaks at δ 2.35 (s, 6 H, 2,6-dimethyls), 2.77 (septet, 1 H, methine proton of 4-isopropyl), 3.42 (septet, 1 H, methine proton of 1-isopropyl), 1.22 (d, 6 H, methyls of 4-isopropyl), 1.35 (d, 6 H, methyls of 1-isopropyl), and 6.78 (s, 2 H, aromatic). The ^{1}H NMR spectrum of 3,5-dimethyl-1,2-diisopropylbenzene showed peaks at δ 2.28 (s, 3 H, 3-methyl), 2.20 (s, 3 H, 5-methyl), 1.22 (d, 6 H, methyls of 1-isopropyl), 1.37 (d, 6 H, methyls of 2-isopropyl), 6.60 (s, 1 H, 4-proton), and 6.75 (s, 1 H, 6-proton). The septet peaks of the methine protons of the 1- and 2-isopropyl groups could not be readily assigned owing to extensive overlapping.

For 2,6-dimethyl-1,4-diisopropylbenzene:

Anal. Calcd for $C_{14}H_{22}$: C, 88.35; H, 11.65. Found: C, 88.39; H, 11.89.

3,5-Dimethyl-4-isopropylacetophenone. 2,6-Dimethyl-1,4-diisopropylbenzene was oxidized to the crude ketone in 56.1% yield by the procedure described for 3,5-dimethyl-4-phenylacetophenone. Purification by preparative VPC (Aerograph instrument, Dow Corning Silicone 550 on Chromosorb W, 180 °C) gave the pure ketone, n^{20}D 1.5350, 2,4-dinitrophenylhydrazone, mp 238–238.5 °C. The ^{1}H NMR spectrum showed peaks at δ 1.31 (d, 6 H, methyls of 4-isopropyl), 3.41 (septet, 1 H, methine proton of 4-isopropyl), 2.38 (s, broad, 9 H, 3,5-dimethyls and acetyl methyl), and 7.32 (s, 2 H, aromatic).

Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.06; H, 9.46.

3,5-Dimethyl-4-isopropyl-α-methylstyrene. 3,5-Dimethyl-4-isopropylacetophenone was treated with methylmagnesium iodide to give an 87.1% yield of the crude carbinol which on purification by preparative VPC (Aerograph instrument, Dow Corning Silicone 550 on Chromosorb W, 180 °C) gave the dehydration product, the olefin, n^{20}D 1.5365. The ^{1}H NMR spectrum showed peaks at δ 1.30 (d, 6 H, methyls of 4-isopropyl), 3.35 (septet, 1 H, methine proton of 4-isopropyl), 2.33 (s, 6 H, 3,5-dimethyls), 2.06 (m, 3 H, α-methyl), 4.87 (m, 1 H, olefinic proton cis of α-methyl), 5.16 (m, 1 H, olefinic proton trans to α-methyl), and 6.86 (s, 2 H, aromatic).

Anal. Calcd for $C_{14}H_{20}$: C, 89.29; H, 10.71. Found: C, 88.99; H, 10.73.

Preparation of Precursors to the Methyl-Substituted 4-Cyclopropyl-*tert*-cumyl Chlorides. 3-Methyl-4-cyclopropylacetophenone. Aluminum chloride catalyzed acetylation of o-methylphenylcyclopropane[60] in anhydrous chloroform at −45 °C gave a 66.6% yield of ketone, bp 112 °C (1 mm), n^{20}D 1.5610, 2,4-dinitrophenylhydrazone, mp 215 °C. VPC analysis (succinate polyester of butanediol, 150-ft capillary, 160 °C) indicated a single product. The ^{1}H NMR spectrum showed an AB pattern at δ 6.92, an AB pattern at δ 7.70 with meta coupling, and a broad doublet at δ 7.78 superimposed upon the δ 7.70 AB pattern.

Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 83.05; H, 8.29.

3-Methyl-4-cyclopropyl-α-methylstyrene. 3-Methyl-4-cyclopropylacetophenone was treated with methylmagnesium iodide to give a 95% yield of the crude carbinol which on purification by preparative VPC (Aerograph instrument, Dow Corning Silicone 550 on Chromosorb W, 180 °C) gave a 52.2% isolated yield of the olefin, n^{22}D 1.5554. The ^{1}H NMR spectrum showed peaks at δ 2.05 (m, 3 H, α-methyl), 2.37 (s, 3 H, 3-methyl), 7.14 (d, 1 H, 2-proton), 7.08 (d, 1 H, 6-proton), 4.93 and 5.24 (m, 2 H, olefinic), 1.54–1.93 (m, 4 H, methylene protons of cyclopropyl), and 0.5–1.0 (m, 1 H, methine proton of cyclopropyl).

Anal. Calcd for $C_{13}H_{16}$: C, 90.64; H, 9.36. Found: C, 90.51; 90.48; H, 9.38; 9.46.

2,6-Dimethylphenylcyclopropane. 2,6-Dimethylstyrene was treated with excess methylene iodide and zinc–copper couple following the LeGoff modification of the Simmons–Smith procedure,[61] except that all of the olefin was added initially to the reaction vessel followed by slow addition of methylene iodide. The product was obtained in 63% yield, bp 54 °C (1 mm), n^{21}D 1.5257. The ^{1}H NMR spectrum showed peaks at δ 2.31 (s, 6 H, 2,6-dimethyls), 6.86 (s, broad, 3 H, aromatic), and 0.20–0.50 and 0.63–0.98 (m, 4 H, methylene protons of cyclopropyl).

Acetylation of 2,6-Dimethylphenylcyclopropane. Aluminum chloride catalyzed acetylation of 2,6-dimethylphenylcyclopropane in anhydrous chloroform at −35 °C gave an 89.9% yield of a mixture separable by preparative VPC (Aerograph instrument, Dow Corning Silicone 550 on Chromosorb W, 180 °C) which consisted of 85% of **2,4-dimethyl-3-cyclopropylacetophenone,** n^{20}D 1.5498, 2,4-dinitrophenylhydrazone, mp 210–211 °C, and 15% of **3,5-dimethyl-4-cyclopropylacetophenone,** n^{20}D 1.5511, 2,4-dinitrophenylhydrazone, mp 234–235 °C. The ^{1}H NMR spectrum of 3,5-dimethyl-4-cyclopropylacetophenone showed peaks at δ 7.43 (s, 2 H, aromatic), 2.41 (s, 9 H, 3,5-dimethyls and acetyl methyl), and 0.38–0.69 and 0.72–1.21 (m, 4 H, cyclopropyl methylene protons).

Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.99; H, 8.54.

The ^{1}H NMR spectrum of 2,4-dimethyl-3-cyclopropylacetophenone showed peaks at δ 6.87 (AB pattern, 1 H, 5-proton), 7.27 (AB pattern, 1 H, 6-proton), 2.47 (s, 3 H), 2.39 (s, 6 H), and 0.80–1.19 and 0.34–0.59 (m, 4 H).

Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.97; H, 8.49.

3,5-Dimethyl-4-cyclopropyl-α-methylstyrene. 3,5-Dimethyl-4-cyclopropylacetophenone was treated with methylmagnesium iodide to give 95.6% yield of the crude carbinol which on purification by preparative VPC (Aerograph instrument, Dow Corning Silicone 550 on Chromosorb W, 180 °C) gave the dehydration product, the olefin, n^{22}D 1.5518. The ^{1}H NMR spectrum showed peaks at δ 2.08 (m, 3 H, α-methyl), 2.40 (s, 6 H, 3,5-dimethyls), 4.93 (m, 1 H, olefinic cis to α-methyl), 5.26 (m, 1 H, olefinic trans to α-methyl), 6.99 (s, 2 H, aromatic), and 0.37–1.18 (m, 4 H, cyclopropyl methylene protons).

Anal. Calcd for $C_{14}H_{18}$: C, 90.26; H, 9.74. Found: C, 90.12; H, 9.58.

Preparation of *p*-Cyclopropyl-Substituted *tert*-Cumyl Chlorides. The chlorides were prepared from the corresponding α-methylstyrene according to the general procedure.[20] In all cases formation of the chloride occurred without opening of the cyclopropyl ring. No olefinic protons were observed in the NMR spectra of the chlorides.

Determination of the Products of Solvolysis of the *p*-Cyclopropyl-Substituted *tert*-Cumyl Chlorides. The solvolyses were conducted in 90% aqueous acetone. The acetone was removed by evaporation from the solution of the solvolyzed chloride, the aqueous layer extracted with ether, and the ether extract washed with aqueous sodium bicarbonate followed by washing with water and then dried over magnesium sulfate. The ether was removed to give the crude solvolysis products.

Each of the solvolysis mixtures was analyzed by two methods: VPC analysis and the correlation in the NMR spectra between observed peak areas and predicted peak areas if the solvolysis mixture consisted of only a single component. The only products observed were the non-ring-opened carbinols and olefins (identified both by VPC retention time and NMR spectrum of authentic samples). The only olefinic protons in the spectra of the solvolysis mixtures were those at the same location and with the same splitting patterns as those in the precursor *p*-cyclopropyl-substituted α-methylstyrenes. No other olefinic components were detected by either analytical method.

Solvolysis in 90% aqueous acetone yielded from 4-cyclopropyl-*tert*-cumyl chloride, 38% alcohol and 62% olefin; from 3-methyl-4-cyclopropyl-*tert*-cumyl chloride, 49% alcohol and 51% olefin; and from 3,5-dimethyl-4-cyclopropyl-*tert*-cumyl chloride, 75% alcohol and 25% olefin.

Registry No.—**7,** 58502-76-4; 3,5-dimethyl-4-cyclopropyl-α-methylstyrene, 58502-77-5; 2-fluorenyl-*tert*-cumyl chloride, 58502-78-6; *p*-isopropylphenyldimethylcarbinol, 3445-42-9; 4-diphenyldimethylcarbinol, 34352-74-4; *p*-cyclopropyl-α-methylstyrene, 19936-10-8; 3-methyl-4-phenyl-α-methylstyrene, 58502-79-7; 3-methyl-4-phenylbromobenzene, 5002-26-6; 5-isopropyl-*m*-xylene, 4706-90-5; aniline, 62-53-3; 3,5-dimethyl-4-phenylisopropylbenzene, 58502-80-0; 3,5-dimethyl-2-phenylisopropylbenzene, 58502-81-1; 3,5-dimethyl-4-phenylacetophenone, 58502-82-2; 3,5-dimethyl-4-phenyl-*tert*-cumyl alcohol, 58502-83-3; methyl iodide, 74-88-4; 2-chloromethyl-1,4-diisopropylbenzene, 58502-84-4; 1,4-diisopropylbenzene, 100-18-5; chloromethyl methyl ether, 107-30-2; 2-methyl-1,4-diisopropylbenzene, 58502-85-5; 3-methyl-4-isopropyl-α-methylstyrene, 58502-86-6; 2,6-dimethyl-1,4-diisopropylbenzene, 42412-93-1; 3,5-dimethyl-1,2-diisopropylbenzene, 58502-87-7; 3,5-dimethyl-4-isopropylacetophenone, 58502-88-8; 3,5-dimethyl-4-isopropylacetophenone 2,4-DNPH, 58502-89-9; 3,5-dimethyl-4-isopropyl-α-methylstyrene, 58502-90-2; o-methylphenylcyclopropane, 27546-46-9; 3-methyl-4-cyclopropylacetophenone, 58502-91-3; 3-methyl-4-cy-

clopropylacetophenone 2,4-DNPH, 58502-92-4; 3-methyl-4-cyclopropyl-α-methylstyrene, 58502-93-5; 2,6-dimethylphenylcyclopropane, 36825-29-3; 2,6-dimethylstyrene, 2039-90-9; 2,4-dimethyl-3-cyclopropylacetophenone, 58502-94-6; 2,4-dimethyl-3-cyclopropylacetophenone 2,4-DNPH, 58502-95-7; 3,5-dimethyl-4-cyclopropylacetophenone, 58502-96-8; 3,5-dimethyl-4-cyclopropylacetophenone 2,4-DNPH, 58502-97-9.

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Copyrolysis of *sym*-Tetramethoxydimethyldisilane and 2,5-Dimethylfuran

Michael E. Childs and William P. Weber*

Department of Chemistry, University of Southern California, University Park, Los Angeles, California 90007

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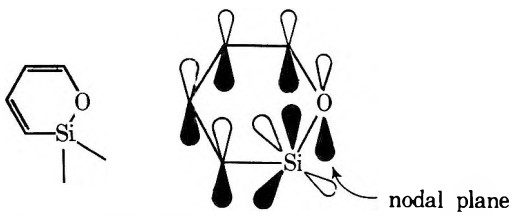
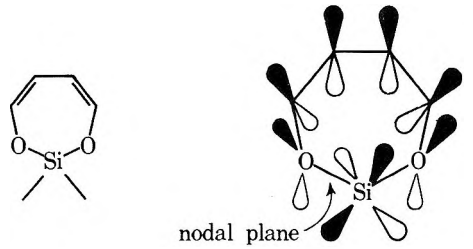
The reaction of methoxymethylsilylene (generated by pyrolysis of *sym*-tetramethoxydimethyldisilane) with 2,5-dimethylfuran yields 2-methoxy-2,3,6-trimethyl-1-oxo-2-silacyclohexa-3,5-diene and 2-methoxy-2,4,7-trimethyl-1,3-dioxo-2-silacyclohepta-4,6-diene.

The synthesis of unsaturated organosilicon heterocycles whose spectral properties might permit elucidation of the extent and nature of the interaction between vacant 3d orbitals on silicon and an adjacent π electron system has attracted considerable interest.[1,2]

The 1-oxo-2-silacyclohexa-3,5-diene (I) system has been a goal of our efforts. Interaction of a lone pair of electrons on oxygen with an empty 3d orbital on silicon and with the diene system would yield a 6π electron system possessing a nodal plane. Such a system is antiaromatic by the Mobius concept.[3,4]

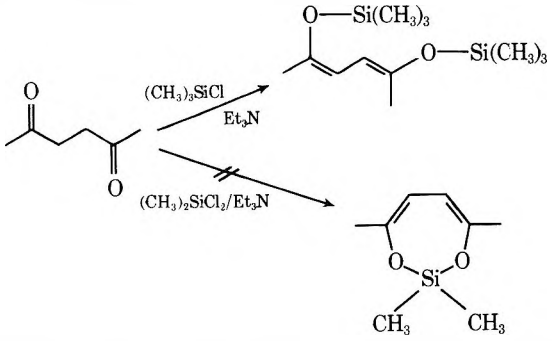


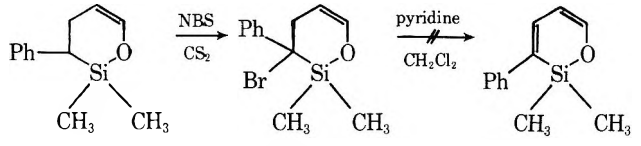
A related goal has been the 1,3-dioxo-2-silacyclohepta-4,6-diene (II) system. Interaction of two lone pairs of electrons from the two oxygens with an empty 3d orbital on silicon and with the diene system yields an 8π electron system possessing a nodal plane. Such a system is aromatic by the Mobius concept.[3,4]



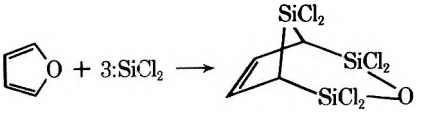
The overlap of pairs of electrons with adjacent empty 3d orbitals on silicon has often been used to explain the properties of compounds possessing adjacent silicon and oxygen atoms.[5,6] Thus the properties of I and II appeared to present an interesting test of this often proposed interaction.

Rational synthetic approaches to both I and II resulted in failure. An attempt to prepare 2,2,4,7-tetramethyl II by reaction of dimethyldichlorosilane with 2,5-hexanedione in the presence of triethylamine,[7] conditions which have been successfully used to prepare the bis(trimethylsilyl)enol ether of 2,5-hexanedione, resulted only in polymer. Attempts to prepare 2,2-dimethyl I by cyclization of suitable alicyclic precursors also failed. While benzylic bromination of 2,2-dimethyl-1-oxo-3-phenyl-2-silacyclohex-5-ene with NBS was easily accomplished,[8] dehydrohalogenation with tertiary amine bases failed to yield the desired 2,2-dimethyl-3-phenyl I.

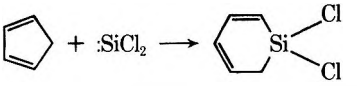




As a last resort, we turned to the reaction of methoxymethylsilylene with 2,5-dimethylfuran as an improbable but direct synthesis of 2-methoxy-2,3,6-trimethyl I. The use of silylenes as synthetic intermediates to prepare compounds which are inaccessible in other ways has been previously reported.[9-14] Nevertheless this approach seemed unlikely for several reasons. Thus although furan is known to react as a 1,3-diene in Diels–Alder reactions[15] it is an aromatic heterocycle and therefore might be expected to be less reactive than most 1,3-dienes as a trapping reagent for silylenes. The reaction of methoxymethylsilylene generated by pyrolysis of *sym*-tetramethoxydimethyldisilane with 1,3-dienes is always a competition between reaction of the silylene with the 1,3-diene, insertion of the silylene into the silicon–oxygen single bonds of *sym*-tetramethoxydimethyldisilane to yield $[CH_3(CH_3O)_2Si]_3SiCH_3$, and finally polymerization of the methoxymethylsilylene.[16-19] In addition, the reaction of dichlorosilylene with furan has been reported to yield an adduct formed from one molecule of furan and three reactive dichlorosilylenes.[20] On the other hand, dichlorosilylene has been

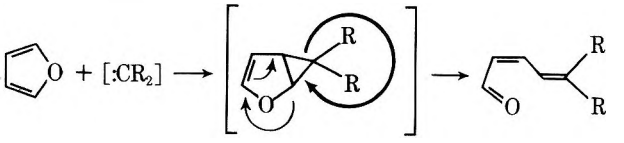


reported to react with cyclopentadiene to yield 1,1-dichloro-1-silacyclohexa-2,4-diene.[20,21] If methoxymethylsilylene reacted with 2,5-dimethylfuran in an analogous manner it would constitute a direct synthesis of 2-methoxy-2,3,6-trimethyl I.



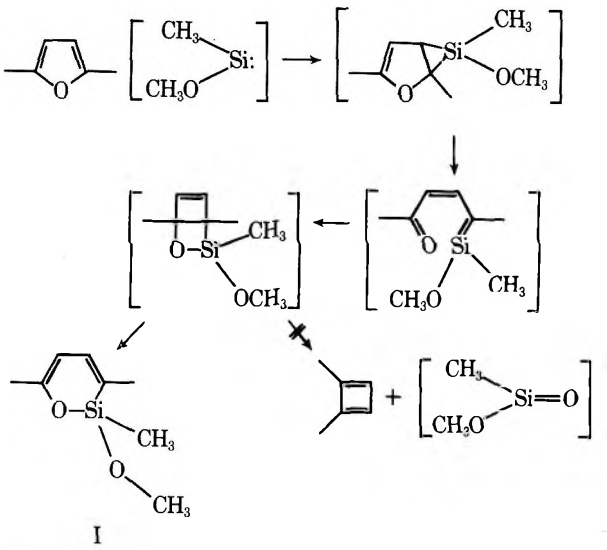
The following experimental conditions were used. *sym*-Tetramethoxydimethyldisilane was used since it undergoes α-elimination to yield methoxymethylsilylene and trimethoxymethylsilane at relatively low temperature.[14,16-19] A flow pyrolysis system was used.[14] The products were rapidly cooled after formation in the hot zone. Experience has shown that prolonged heating of products is undesirable. 2,5-Dimethylfuran was chosen since the methyl groups would be expected to retard further condensation reactions.

2-Methoxy-2,3,6-trimethyl I was isolated from the copyrolysis reaction of *sym*-tetramethoxydimethyldisilane and 2,5-dimethylfuran. However, the yield of 2-methoxy-2,3,6-trimethyl I was never better than a few percent based on methoxymethylsilylene generated, despite numerous attempts at modification of experimental parameters. A possible mechanism for the formation of 2-methoxy-2,3,6-trimethyl I may be formulated on the basis of analogous carbene chemistry. Carbenes add to furan to yield 2,4-dien-1-one systems. This result has been explained in terms of initial addition of the carbene to one of the carbon–carbon double bonds of the furan to form an unstable vinyl cyclopropane which undergoes ring opening.[22,23] By analogy, addition of



methoxymethylsilylene to one of the carbon–carbon double bonds of 2,5-dimethylfuran yields an unstable vinyl silacyclopropane intermediate.[17,24,25] Ring opening in an analogous manner yields an intermediate possessing a reactive silicon–carbon double bond. A [2 + 2] intramolecular cycloaddition reaction between the silicon–carbon double bond and the carbonyl group yields a 1,2-silaoxetane. Intermolecular [2 + 2] cycloaddition reactions of silicon–carbon doubly bonded intermediates and ketones have been proposed.[8,26-28] Ring opening of the 1,2-silaoxetane yields 2-methoxy-2,3,6-trimethyl I. This is *not* the usual fragmentation pathway of a 1,2-silaoxetane intermediate which would be expected to yield methoxymethylsilanone and 1,2-dimethylcyclobutadiene. The strain and instability of 1,2-dimethylcyclobutadiene may disfavor the usual fragmentation pathway.

However, an additional unexpected product was also isolated from the reaction, namely, 2-methoxy-2,4,7-trimethyl



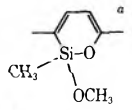
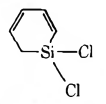
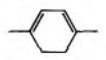
I

II. Pathways for its formation are purely speculation at this time. It is formed in 1.5% yield based on methoxymethylsilylene generated. Certainly, 2,5-dimethylfuran is not a reactive trapping agent for methoxymethylsilylene.[16-19]

Finally, what are the properties of 2-methoxy-2,3,6-trimethyl I and 2-methoxy-2,4,7-trimethyl II? Is 2-methoxy-2,3,6-trimethyl I an antiaromatic system and 2-methoxy-2,4,7-trimethyl II an aromatic system as predicted by the Mobius concept? The answer to this question may test the assumption underlying the prediction, namely that empty 3d orbitals on silicon interact appreciably with filled 2p orbitals on adjacent carbon or oxygen atoms.

A problem in attempting to answer this question is a shortage of material owing to the low yields of both 2-methoxy-2,3,6-trimethyl I and 2-methoxy-2,4,7-trimethyl II obtained. Thus we will rely on comparison of their spectroscopic properties with those of model compounds. On the basis of ultraviolet spectra both 2-methoxy-2,3,6-trimethyl I and 2-methoxy-2,4,7-trimethyl II seem quite ordinary. (See Tables I and II for data.) Thus we would conclude that overlap of empty 3d orbitals on silicon with adjacent 2p orbitals on oxygen or carbon is unimportant even in cyclic systems where symmetry and theory predict that stabilization will result from such overlap. Study of the effect of silyl substitution on the inversion barriers of amines and phosphines has resulted in similar conclusions.[29-31]

Table I. Ultraviolet Spectra of 2-Methoxy-2,3,6-trimethyl I and Model Compounds

Compd	λ_{max}, Å	ϵ	Solvent	Ref
 [a]	2730	8500	Cyclohexane	This work
	2820	3900	Ethanol	32
	2650	Extinction coefficient and solvent not specified		33
	2640	7420	Solvent not specified	34

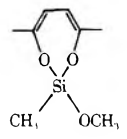
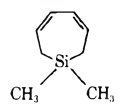
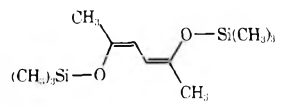
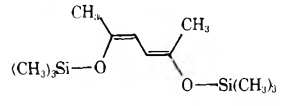
[a] Registry no., 58449-10-8.

Experimental Section

Infrared spectra were obtained on a Perkin-Elmer 337 spectrometer and were calibrated against known bands in a polystyrene film. NMR spectra were recorded on a Varian T-60 or XL-100 spectrometer. Spectra were taken using 10% solutions in carbon tetrachloride with benzene or acetone as internal standard. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6E spectrometer at an ionizing voltage of 70 eV. High-resolution mass spectra were obtained on a AEI-MS-9. Exact mass determinations of the compositions of ions were carried out at a resolution of at least 15 000 by peak matching with peaks of known mass of perfluorokerosene at 70 eV. Vapor phase chromatography was carried out on a Hewlett Packard F & M 700. Microanalysis was performed by Elek Microanalytical Laboratories, Torrance, Calif. Boiling points are not corrected.

Copyrolysis of 2,5-Dimethylfuran and *sym*-Tetramethoxydimethyldisilane. The pyrolysis apparatus has been described previously.[14] The oven was heated to 410 °C. A mixture of 5.1 g (0.024 mol) of *sym*-tetramethoxydimethyldisilane and 14.9 g (0.155 mol) of freshly distilled 2,5-dimethylfuran was placed in an addition funnel. The nitrogen flow rate was adjusted to 1 ml/s. The mixture was added to the pyrolysis tube at a rate of 1 drop every 10 s. A flow of nitrogen gas was continued through the column for 30 min after completion of the addition. The material from the two cold traps was combined (19.0 g). One gram of material was lost on the column. Recovered 2,5-dimethylfuran (14.1 g, 0.147 mol) and trimethoxymethylsilane (2.4 g, 0.018 mol) were removed by distillation through a 15-cm Vigreux column. A single fraction, bp 90–100 °C (760 mm), was collected. Its composition was determined by NMR integration and GLC on a 15 ft × 0.25 in., 10% polyphenyl ether on Chromosorb P column at 110 °C. Thus 75% of the starting *sym*-tetramethoxydimethyldisilane has

Table II. Ultraviolet Spectra of 2-Methoxy-2,4,7-trimethyl-II and Model Compounds

Compd	Registry no.	λ_{max}, Å	ϵ	Solvent	Ref
	58449-11-9	2480	10500	Cyclohexane	This work
		2480	7500	Not specified	35
		2470	3000	Cyclohexane	36
	58449-12-0	2520	21000	Cyclohexane	This work
	58449-13-1	2520	12200	Cyclohexane	This work

reacted to yield methoxymethylsilylene and trimethoxymethylsilane. The pot residue (2.4 g) was bulb to bulb distilled at 0.5 mm. In this manner 1.2 g of clear, slightly yellow liquid was obtained. The pot residue (1.2 g) was a thick, yellow, nonvolatile oil whose NMR indicated only CH_3Si and CH_3OSi signals in a 1:1 ratio by integration. Thus the pot residue must be polymers of methoxymethylsilylene. The pot residue (1.2 g) amounts to 0.0176 mol of methoxymethylsilylene. Thus of the methoxymethylsilylene produced greater than 90% undergoes polymerization. Separation of the volatile yellow liquid (1.2 g) by preparative GLC, on the same column as above, at 140 °C gave 2-methoxy-2,3,6-trimethyl I (0.1 g, 0.59 mmol) in 3.3% yield and 2-methoxy-2,4,7-trimethyl II (0.05 g, 0.27 mmol) in 1.5% based on the amount of methoxymethylsilylene produced. In addition unreacted *sym*-tetramethoxydimethyldisilane (0.24 g, 1.2 mmol) as well as higher molecular weight products of insertion of methoxymethylsilylene into the Si–O bond of *sym*-tetramethoxydimethyldisilane were observed.[16-19]

2-Methoxy-2,3,6-trimethyl-I. Samples were purified by preparative GLC on a 6 ft × 0.25 in., 10% β,β-ODPN on Chromosorb P column at 80 °C from material which had been collected from the polyphenyl ether column above. It had the following spectral properties: NMR, s (3 H) δ 0.25, s (3 H) 1.84, s (3 H) 1.88, s (3 H) 3.30, d (1 H) 4.93, J = 6 Hz, and d (1 H) 6.43, J = 6 Hz; ir (CCl_4) Si–CH_3 1220 and 830 cm^{-1}, Si–O and C–O 1100, 1080, and 1016 cm^{-1}, and C=C 1630 cm^{-1}; mass spectrum (70 eV) parent ion at *m/e* 170 (100%), P − CH_3 at *m/e* 155 (90.4%), and P − OCH_3 at *m/e* 139 (66.7%); uv (cyclohexane) λ_{max} 2730 Å, ε 8500. Anal. Calcd for $C_8H_{14}O_2Si$: C, 56.43; H, 8.29. Found: C, 56.29; H, 8.22.

2-Methoxy-2,4,7-trimethyl-II. Samples were purified by preparative GLC on a 10 ft × 0.25 in., 20% Ucon Polar on Chromosorb P column at 135 °C from material which had been collected from the polyphenyl ether column above. It had the following spectral properties: NMR, s (3 H) δ 0.20, s (6 H) 1.90, s (3 H) 3.65, s (2 H) 4.70; ir (CCl_4) Si–CH_3 1265 cm^{-1}, Si–O and C–O 1100 and 1185 cm^{-1}, and C=C 1650 cm^{-1}; uv (cyclohexane) λ_{max} 2480 Å, ε 10 500; mass spectrum (70 eV) parent ion at *m/e* 186 (100%), P − CH_3 at *m/e* 171 (20%); high-resolution mass spectrum, the exact mass of the parent ion (calcd for $C_8H_{14}O_3Si$, 186.07122; found, 186.0713).

Preparation of *cis*- and *trans*-2,5-Bis(trimethylsiloxy)-2,4-hexadiene. In a dry three-neck 500-ml round-bottom flask equipped with a reflux condenser, a Teflon-covered magnetic stirring bar, and a nitrogen inlet was placed 100 ml of dimethylformamide (freshly distilled from CaH_2), trimethylchlorosilane (27.0 g, 0.25 mol), and triethylamine (47.0 g, 0.43 mol).[7] 2,5-Hexanedione (10.0 g, 0.095 mol) was added through the top of the reflux condenser. White fumes and a yellow solid rapidly formed. The mixture was refluxed for 72 h. It was cooled and 200 ml of pentane was added. The solution was placed in a separatory funnel and extracted three times with 200-ml portions of aqueous $NaHCO_3$. The organic layer was dried over anhydrous $MgSO_4$, filtered, and the volatile solvents removed by evaporation under reduced pressure. The residue was distilled through a 12-cm vacuum-jacketed Vigreux column. A fraction bp 125–126 °C (25 mm) was collected (13.0 g, 53%). The mixture of isomers was separated by GLC on a 20% polyphenyl ether on Chromosorb P, 25 ft × 0.25 in. column at 140 °C. The more symmetrical trans isomers eluted first.

***trans*-2,5-Bis(trimethylsiloxy)-2,4-hexadiene** had the following spectral properties: NMR s (18 H) δ 0.1, s (6 H) 1.65, s (2 H) 5.18; ir Si–CH_3 1250 and 850 cm^{-1}, Si–O and C–O at 1160 cm^{-1}, and C=C conjugated at 1615 cm^{-1}. High-resolution mass spectrum, the exact mass of the parent ion (calcd for $C_{12}H_{26}Si_2O_2$, 258.1464; found, 258.1471). Anal. Calcd for $C_{12}H_{26}Si_2O_2$: C, 55.74; H, 10.14. Found: C, 55.11; H, 9.74.

***cis*-2,5-Bis(trimethylsiloxy)-2,4-hexadiene** had the following spectral properties: NMR s (18 H) δ 0.1, s (3 H) 1.62, s (3 H) 1.67, d (1 H) 4.98, J = 12 Hz, d (1 H) 5.38, J = 12 Hz; ir Si–CH_3 1250 and 850 cm^{-1}, Si–O and C–O 1212 and 1175 cm^{-1}, and C=C conjugated at 1615 cm^{-1}. Anal. Calcd for $C_{12}H_{26}O_2Si_2$: C, 55.74; H, 10.14. Found: C, 55.36; H, 9.89.

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Registry No.—2,5-Dimethylfuran, 625-86-5; *sym*-tetramethoxydimethyldisilane, 18107-32-9.

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Synthesis of Adamantane Derivatives. 32.[1] The Beckmann Rearrangement and Fragmentation Aptitude of Noradamantan-2-one Oxime

Tadashi Sasaki,* Shoji Eguchi, and Osamu Hiroaki

Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, 464, Japan

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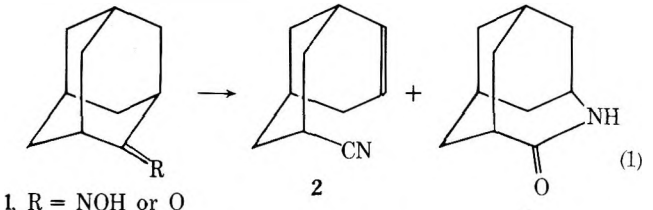
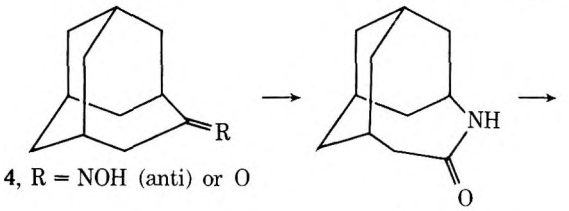
The Beckmann rearrangement of noradamantan-2-one oxime (syn and anti ratio 33:67) by polyphosphate ester afforded 4-azaprotoadamantan-5-one (**9**) and 5-azaprotoadamantan-4-one (**10**) as normal ring-expansion products and 3-cyanobicyclo[3.2.1]oct-6-ene (**11**), 6-cyano- (**12**), and 7-cyanobicyclo[3.2.1]oct-2-ene (**13**) as fragmentation products. The product distribution was time dependent, and **9** and **10** were converted to **11**–**13** under the reaction conditions. The fragmentation aptitude of noradamantan-2-one oxime and lactams **9** and **10** was rationalized from antiperiplanarity in the units H–C–C–C=N$^+$ or H–C–C–N=C$^+$ and strain considerations.

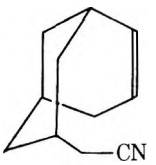
In the Beckmann and Schmidt reactions, the adamantanone (**1**) gives mainly the fragmentation product **2**[2] accompanied by the normal rearrangement product **3** (eq 1).[3] By comparison homoadamantan-4-one (**4**) affords exclusively normal rearrangement product **5** (or its regioisomer) which is, however, not stable under the reaction conditions and gives nitrile **6** in the Beckmann rearrangement by polyphosphate ester (PPE), and tetrazole derivatives in the Schmidt reaction (eq 2).[4] In view of this interesting behavior of caged ketone systems in the Beckmann and Schmidt reactions we were interested in the behavior of the noradamantan-2-one (**7**) system. This paper describes the results of the Beckmann rearrangement of **7**-oxime.



1, R = NOH or O **2** **3** (1)



4, R = NOH (anti) or O **5**



6 (2)

Results and Discussion

Oximation of noradamantan-2-one (**7**)[5] in 50% aqueous ethanol in the presence of excess potassium hydroxide afforded a 33:67 mixture of syn (**8s**) and anti oxime (**8a**)[6] in 74% yield after one recrystallization. The syn and anti ratio was determined by NMR data in the presence of a shift reagent, Eu(dpm)$_3$ (see Experimental Section).[7]

Treatment of **8s** and **8a** (33:67) in chloroform with a large excess of PPE under reflux afforded products **9**–**13** in a 23.4:40.0:4.3:16.9:15.6 ratio on GLC analysis (99.6% conversion). These products were isolated after chromatography (silica gel) and preparative GLC, and their structures were determined as summarized in Scheme I.

Both **9** and **10** were obtained as crystalline solids. In the ir spectra (KBr), **9** had strong absorptions at 3200 (NH) and 1665 cm^{-1} (C=O) and **10** at 3220 (NH) and 1644 cm^{-1}

Scheme I

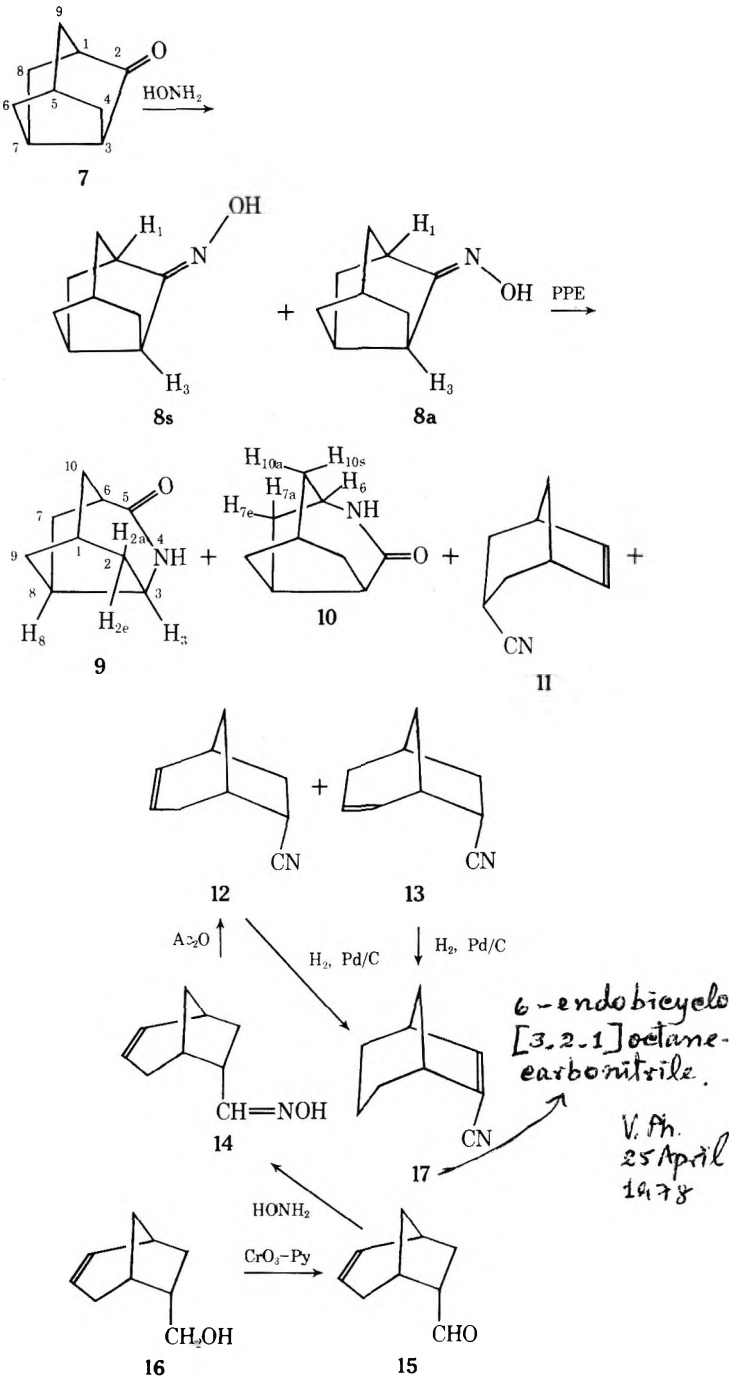


Table I. Observed and Calculated Coupling Constants for H_3 of 9 and H_6 of 10

H_3 of 9	Obsd, Hz	Calcd, Hz	(Dihedral angle)	H_6 of 10	Obsd, Hz	Calcd, Hz	(Dihedral angle)
$J_{2e,3}$	7.5	6.7	(25°)	$J_{6,7e}$	0	0.3	(75°)
$J_{2a,3}$	0	0	(95°)	$J_{6,7a}$	3.0	3.8	(45°)
$J_{3,8}$	7.5	7.9	(10°)	$J_{6,10s}$	0	0	(80°)
				$J_{6,10a}$	3.0	3.8	(45°)

Table II. Product Distributions of the Beckmann Rearrangement of 8s + 8a[a]

Reagent (amount)	Solvent	Temp °C	Time, min	Conversion, %[b]	Product distribution, %[b] 9	10	11	12	13	Others
PPE (20 w/w)	*$CHCl_3$*	*Reflux*	0.5	8.9	34.1	44.2	0.7	11.0	10.0	0
			5	42.3	31.6	43.7	1.7	12.8	10.2	0
			20	66.6	30.0	42.8	3.0	13.4	10.8	0
			50	87.9	30.5	45.1	3.5	14.6	13.1	0
			100	99.3	27.9	36.5	4.3	17.8	13.5	0
				(99.8)[c]	(25.7)	(41.7)	(4.0)	(16.2)	(12.4)[c]	Trace[d]
TsCl (1.2 mol)	$HCONMe_2$	80	240	17.8	1.2	25.8	3.9	50.0	10.1	8.9[d]
PCl_5 (4.0 mol)	Et_2O	r.t.[e]	2400	87.6	0.5	1.2	9.8	20.3	7.3	60.9[d]
NaN_3[f] (2.0 mol)	$MeSO_3H$–AcOH[g]		240	93.8	25.4	15.4	9.9	43.5	3.1	2.8[d]

[a] A 33:67 mixture was used. [b] GLC analysis. [c] Isolated yield. [d] Unidentified. [e] Ca. 25 °C. [f] The Schmidt reaction of 7. [g] 1:9 v/v ratio.

(C=O), indicating that 9 and 10 are isomeric lactams and normal rearrangement products. In the NMR spectra, 9 had a characteristic double triplet (J = 5.0 and 7.5 Hz) at δ 3.85 (1 H) assignable to CHNHCO–, which changed to a triplet (J = 7.5 Hz) on deuteration, while 10 had a pentet (J = 3.0 Hz) at δ 3.45 (1 H) which became a triplet (J = 3.0 Hz) on deuteration. The observed coupling constants and those calculated for H_3 of 9 and H_6 of 10 based on a Karplus relationship[8] and dihedral angles for C_3–H_3 and C_6–H_6 (on a Dreiding stereomodel) are summarized in Table I. From comparison of these values 9 was assigned as 4-azatricyclo[4.3.1.$0^{3,8}$]decan-5-one (or trivially 4-azaprotoadamantan-5-one) and 10 as *5-azatricyclo[4.3.1.$0^{3,8}$]decan-4-one (or 5-azaprotoadamantan-4-one)*.

Compounds 11–13 were obtained as volatile, oily materials after purification on preparative GLC, and had the same formula $C_9H_{11}N$. Ir spectra of 11–13 exhibited absorptions at 2245, 2240, and 2240 cm^{-1}, respectively, due to a nitrile function, suggesting that these compounds are the Beckmann fragmentation products. Treatment of 9 with PPE in chloroform under reflux for 600 min gave nitrile 11 (1.5%); the same reaction with 10 gave 12 and 13 (36.2%, 97:3 ratio).

Nitrile 11 had NMR signals at δ 6.55 (broad s, 2 H), 4.65–3.75 (m, 3 H), and 1.6–1.1 (m, 6 H), and hence the structure was assigned as 3-*endo*-cyanobicyclo[3.2.1]oct-6-ene. The *endo configuration of the 3-CN group was assigned on the* basis of its formation from 9 and the appearance of two vinyl proton signals at somewhat lower field than that of norbornene derivatives (δ 6.25–5.85)[9] (due to the anisotropy effect of the CN group).[10]

Nitriles 12 and 13 had very similar NMR spectra which revealed two vinylic protons signals at δ 5.4–5.9 and other protons signals at δ 3.3–1.0. Both 12 and 13 afforded the same dihydro derivative 17 on catalytic hydrogenation (Pd/C), indicating that both 12 and 13 have the same carbon skeleton. Their formation from 10 suggested that 12 and 13 are 6-*endo*- or 7-*endo*-cyanobicyclo[3.2.1]oct-2-ene. Finally, 12 was determined as 6-*endo*-cyanobicyclo[3.2.1]oct-2-ene and hence *13 as 7-endo-cyanobicyclo[3.2.1]oct-2-ene by an alternative* synthesis of 12 via 14 and 15 starting from 16, which has been reported previously by us[11] (Scheme I).

The material balance observed in the Beckmann rearrangement of 8s + 8a (33:67) was in accord with the well-known fact that the trans group with respect to oxime hydroxyl group migrates to afford lactams in the Beckmann rearrangement,[12] and hence it can be concluded that 9 and 11 originate from 8s, while 10, 12, and 13 arise from 8a, respectively (eq 3 and 4).

$$8s \rightarrow 9 + 11 \quad (3)$$

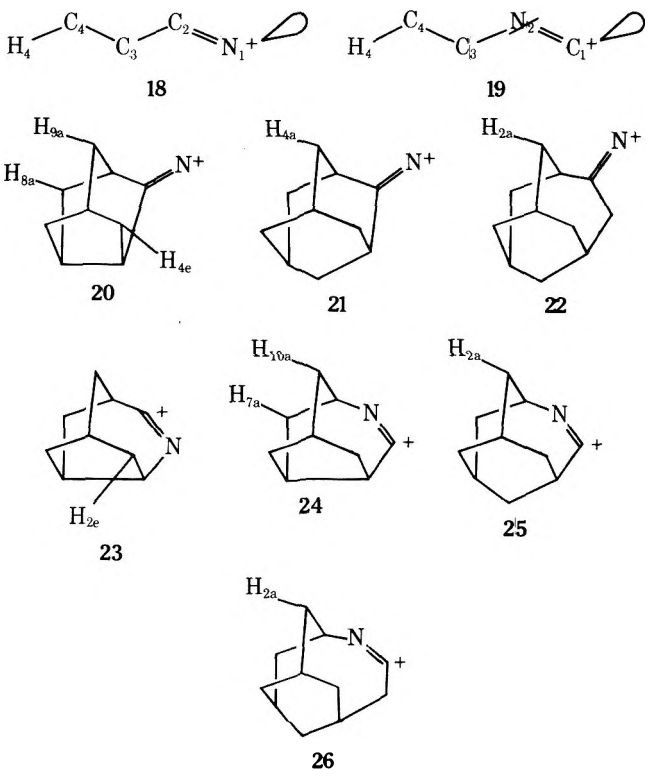
$$8a \rightarrow 10 + 12 + 13 \quad (4)$$

Since fragmentation to nitriles was observed extensively in the Beckmann rearrangement of 8s and 8a even with PPE, some other conditions were also examined and the results are summarized in Table II as well as the product distributions at various reaction times. The rearrangement with *p*-toluenesulfonyl chloride (TsCl) in dimethylformamide at 80 °C gave only very low conversion, but fragmentation products were produced extensively. Phosphorus pentachloride in ether also did not improve the results. For comparison, one example of the Schmidt reaction of 7 under very mild conditions is also shown in Table II. Extensive fragmentation was also observed.[13] In the reaction with PPE the fragmentation products 11–13 were produced even at very short reaction time, indicating that synchronous fragmentation paths as well as rearrangement–fragmentation paths are involved.[14] However, as the relative ratio of products in Table II shows, the fragmentation aptitudes of 8s and 8a as well as those of lactams 9 and 10 or their corresponding iminium cations[15] are quite different. Such difference may be ascribable to the degree of deviation from the antiperiplanarity of the participating bonds in the H–C–C–C=N moiety as postulated by Grob[14] and in a recent theoretical study.[16] For the indirect fragmentation, inductive and steric effects may be important factors.[14] As a simple method for expression of the deviation from the ideal antiperiplanarity, we measured values defined by $(180 - \phi) + \theta$ for each hydrogen, in which ϕ is the dihedral angle defined by bonds C_2–C_3 (or N_2–C_3) and C_4–H_4, and θ is the angle between bond C_4–H_4 and a plane involving bond C_2–C_3 (or N_2–C_3) and vertical to a C_2, C_3, C_4 (or N_2, C_3, C_4) plane in 18 and 19.[17] The values for related hydrogens in 20–26 were

Table III. Deviations from Antiperiplanarity on Dreiding Stereomodel

Model str	20	20	20	21	22[c]	23	24	24	25	26[c]
Hydrogen	H_{4e}	H_{8a}	H_{9a}	H_{4a}	H_{2a}	H_{2e}	H_{7a}	H_{10a}	H_{2a}	H_{2a}
180-φ, deg[a]	17	14	6	0	22	37	14	17	18	36
θ, deg[a]	10	5	7	0	6	7	7	0	5	0
Deviation, deg[b]	27	19	13	0	28	44	21	13	23	36

[a] For the definition, see text. [b] $(180 - \varphi) + \theta$. [c] Assuming an untwisted conformation.



measured on a Dreiding stereomodel by using an imine component for C=N$^+$ or N=C$^+$ and are summarized in Table III. For example, H_{4e} in **20** is the hydrogen to be lost in the **8s** → **11** conversion. Of two hydrogens such as H_{4e} and H_{4a} in **20**, only H_{4e}, having a smaller deviation from antiperiplanarity, is shown in Table III. Comparison of the deviation for H_{4e}, H_{8a}, and H_{9a} in **20** indicates that the fragmentation should decrease in the order **8a** → **12** > **8a** → **13** > **8s** → **11**, as observed (Table II). H_{4a} in **21** (adamantanone system) has the ideal geometrical arrangement as postulated previously, and in fact, its large fragmentation aptitude is well known.[3,18] For the homoadamantan-4-one system with a flexible ethano bridge[19] an accurate value for the deviation could not be measured but approximate values for $(180 - \phi)$ and θ are 22 and 6° assuming an untwisted conformation (**22**). These deviations are considerably larger, in accord with their corresponding negative fragmentation aptitude.[4]

For the indirect fragmentation, the degree of deviation does not seem an important factor for determining the fragmentation aptitude: H_{2e} in **23** has a considerably larger deviation value but its fragmentation (**9** → **11**) was observed, while H_{2a} in **25** has much less deviation and yet the fragmentation of 4-azahomoadamantan-5-one (**3**) to 7-*endo*-cyanobicyclo-[3.3.1]non-2-ene (**2**) was not observed with PPE.[4b] There is a possibility that the fragmentation may be facilitated by inductive effects in the derived olefins;[20] the double bond in **11** (from **23**) is substituted by two secondary alkyl groups, while that in **2** (from **25**, if formed) is substituted by one secondary alkyl and one primary alkyl group, and hence **23** (or **9**) → **11** conversion becomes possible despite the larger "deviation" value. However, a facile fragmentation of **5** to **6** (eq 2)[4b] with PPE cannot be rationalized by such differences in inductive effects since both **2** and **6** have the same primary and secondary substituents for the double bond. Examination of **26** assuming an untwisted conformation[21] (Table III) indicates that the deviation value is considerably larger than that for **25**. In these indirect fragmentations, another important factor may be ring strain because the most fragmentable intermediate (**26**) is considered to involve the largest ring strain and the fragmentable intermediates **23** and **24** have less strains based on values reported for saturated carbocyclic analogues.[22] On the other hand, the observed large regioselectivity in the fragmentation of **10** (eq 4), i.e., almost exclusive formation of the 6-cyano derivative **12** rather than the 7-cyano **13**, should be ascribable to the deviation values because inductive and strain factors are the same.

In summary the deviation values from antiperiplanarity of H_4–C and C_2–C_3 in **18** are useful for estimation of the direct Beckmann fragmentation aptitude of rigid caged ketone systems, while those of H_4–C_4 and N_2–C_3 in **19** are important for determining the regioselectivity of the indirect fragmentation.

Experimental Section[23]

Noradamantan-2-one (7). This was prepared by the method of Nickon and his co-workers.[5] Deltacyclane[5c] (1.472 g, 12.3 mmol) in *n*-pentane (5 ml) was treated with 96% sulfuric acid (77 ml) at −10 to 5 ° for 16 min. Hydrolysis of the mixture and sublimation afforded noradamantan-2-ol (1.496 g, 88.4%), mp 218–219 °C (lit.[5a] 221–222 °C), which was oxidized to noradamantan-2-one (**7**), mp 214–215 °C (lit.[5a] 214.5–215 °C) with the Brown reagent[24] in 85% yield.

Noradamantan-2-one Oxime (8s + 8a). A mixture of **7** (1.686 g, 12.4 mmol) and hydroxylamine hydrochloride (1.034 g, 14.9 mmol) in ethanol (20 ml) and aqueous KOH [85%, 4.18 g in water (20 ml)] was refluxed for 3 h. The cooled mixture was concentrated to ca. 30 ml and neutralized with 5% hydrochloric acid to afford crude oxime as colorless precipitates which was recrystallized from water to give a 33:67 mixture of syn (**8s**) and anti oxime (**8a**) (1.388 g, 74.2%): mp 107.5–109.5 °C; ir (KBr) 3230, 3140, 2930, 2870, 1681, 1472, 1456, 1080, 970, 950, 910, 794, and 775 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 8.65 (broad s, 1 H, disappeared on shaking with D_2O), 3.50 (d, d, $J_{3,7}$ = 7.0, $J_{2,3}$ = 6.0 Hz, 0.67 H, H_3 of **8a**), 2.60 (broad s, 0.33 H, H_1 of **8s**), 2.30 (m, 2 H), and 2.0–1.2 (m, 8 H); in the presence of Eu(dpm)$_3$ [the mole ratio of Eu(dpm)$_3$ to **8s** + **8a** = 0.140], H_3 of **8a** and **8s** appeared at δ 5.45 and 4.41 in 2:1 ratio as the similar unsymmetrical triplet (J = ca. 6.5 Hz), and H_1 of **8a** and **8s** at δ 4.29 and 5.10, respectively, as a broad singlet (in 2:1 ratio);[7] mass spectrum *m/e* 151 (M^+).

Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.33; H, 8.64; N, 9.06.

Beckmann Rearrangement of 8s and 8a with PPE. A 33:67 mixture of **8s** and **8a** (0.860 g, 5.63 mmol) and PPE[25] (17.2 g, 20 w/w times to the oxime) in chloroform (15 ml) was refluxed for 100 min. The cooled mixture was diluted with water (50 ml) and stirred for 24 h at room temperature. After neutralization with 10% KOH, the mixture was extracted with CH_2Cl_2 (7 × 10 ml). The combined extracts were dried (Na_2SO_4) and concentrated to ca. 1 ml. GLC analysis (Silicone SE-30 column, 100 and 170 °C) revealed seven peaks in the ratio 23.3:39.8:4.3:0.4:16.8:15.5:trace corresponding to lactams **9** and **10**, nitrile **11**, ketone **7**, nitriles **12** and **13**, and oxime, respectively. Chromatography on a silica gel column eluting with *n*-hexane–CH_2Cl_2 afforded **3-*endo*-cyanobicyclo[3.2.1]oct-6-ene (11)** as the first fractions (32 mg, ca. 5% of **7** was contaminated, 4.0%). Pure **11** was obtained as a semisolid after preparative GLC (30% Silicone SE-30 on 45/60 mesh Chromosorb W, at 120 °C): ir ($CDCl_3$) 3000, 2940, 2920, 2245, 1280, 1037, 984, and 890 cm^{-1}; NMR, see text; mass spectrum mol wt 133.0885 (calcd for $C_9H_{11}N$, 133.0889). The second fractions were a 57:43 mixture of **6-*endo*-cyano-(12)** and **7-*endo*-cyanobicyclo[3.2.1]oct-2-ene (13)** (214 mg) which was purified by prepar-

ative GLC. **12** was obtained as an oil: $n^{24}D$ 1.5027; ir (neat) 3033, 2920, 2882, 2850, 2240, 1460, and 741 cm^{-1}; NMR ($CDCl_3$) δ 5.97 (m, 1 H), 5.50 (m, 1 H), and 3.3–1.0 (m, 9 H); mass spectrum *m/e* (rel intensity) 134 (10.2), 133 (M^+, 50.2), 132 (35.6), 104 (10.7), 93 (13.6), 92 (16.7), 91 (22.2), 81 (15.6), 80 (100), and 79 (74).

Anal. Calcd for $C_9H_{11}N$: C, 81.16; H, 8.31; N, 10.52. Found: C, 81.31; H, 8.15; N, 10.56.

Nitrile **13** was obtained as a semisolid: ir (neat) 3030, 2920, 2880, 2850, 2240, 1460, 1445, and 710 cm^{-1}; NMR ($CDCl_3$) δ 5.86 (m, 1 H), 5.42 (m, 1 H), and 3.25–1.2 (m, 9 H); mass spectrum *m/e* (rel intensity) 134 (4.5), 133 (M^+, 30.2), 132 (17.8), 91 (14.6), 80 (100), and 79 (8.5).

Anal. Calcd for $C_9H_{11}N$: C, 81.16; H, 8.31; N, 10.52. Found: C, 81.35; H, 8.40; N, 10.35.

The third fractions gave a trace of unreacted oxime and the fourth fractions afforded **4-azaprotoadamantan-5-one (9)** as a hygroscopic solid (218 mg, 25.6%) which was purified by recrystallization from *n*-hexane–CH_2Cl_2: mp 274–276 °C; ir (KBr) 3200, 3100, 3050, 2940, 2910, 2860, 1665, 1482, 1458, 1445, 1415, 1344, 1308, 1283, 1177, 1148, 834, 818, 792, and 660 cm^{-1}; NMR ($CDCl_3$) δ 6.25 (broad s, 1 H, disappeared on shaking with D_2O, NH), 3.85 (t, d, J = 7.5 and 5.0 Hz, t on deuteration, 1 H), 2.50 (m, 2 H), 2.25 (m, 1 H), and 2.0–1.5 (m, 8 H); mass spectrum *m/e* (rel intensity) 152 (15.2), 151 (66.7), 150 (16.7), 124 (21.2), 123 (85.0), 122 (27.3), 119 (15.2), 111 (13.0), 110 (18.4), 109 (31.8), 108 (30.3), 106 (15.2), 105 (21.2), 104 (12.1), 97 (18.3), 96 (21.2), 95 (27.3), 94 (23.2), 93 (24.2), 92 (10.9), 91 (25.8), 85 (21.2), 83 (23.2), 82 (35.4), 81 (42.5), 80 (100), and 79 (45.5).

Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.47; H, 8.68; N, 9.26.

The fifth fractions gave **5-azaprotoadamantan-4-one (10)** as a hygroscopic solid (354 mg, 41.6%) which was purified by sublimation and recrystallization from *n*-hexane: mp 251–253 °C; ir (KBr) 3220, 3040, 2930, 2870, 1644, 1445, 1330, 1290, 1277, 1225, 1162, 1138, 1110, 1070, 993, 978, 910, 854, 763, 738, and 660 cm^{-1}; NMR ($CDCl_3$) δ 6.80 (broad s, disappeared on shaking with D_2O, 1 H, NH), 3.45 (pentet, J = 3.0 Hz, t on deuteration, 1 H), 2.65 (m, 2 H), 2.35 (m, 1 H), and 2.1–1.5 (m, 8 H); mass spectrum *m/e* (rel intensity) 152 (15.0), 151 (M^+, 62.1), 150 (14.5), 136 (20.8), 134 (12.0), 133 (12.5), 123 (22.3), 122 (16.1), 121 (14.7), 110 (16.5), 109 (86.3), 108 (56.0), 104 (29.1), 97 (13.0), 96 (18.6), 95 (32.0), 93 (22.0), 91 (23.8), 83 (15.0), 81 (44.0), 80 (48.5), and 40 (100).

Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.65; H, 8.81; N, 9.08.

The product distributions at various reaction times were determined by GLC after extractions with CH_2Cl_2 of the hydrolyzed and neutralized reaction mixtures at appropriate reaction times.

In another run, nitrile mixture was directly purified on preparative GLC.

Beckmann Rearrangement of 8s and 8a with *p*-Toluenesulfonyl Chloride. A 33:67 mixture of **8s** and **8a** (15 mg, 0.10 mmol) and *p*-toluenesulfonyl chloride (23 mg, 1.2 mmol) in dimethylformamide (1.0 ml) was stirred at 80 °C for 4 h. The cooled mixture was diluted with water (10 ml) and extracted with methylene chloride (5 × 3 ml). The combined extracts were washed with water and dried (Na_2SO_4) and concentrated to ca. 1 ml which was analyzed on GLC.

Beckmann Rearrangement of 8s and 8a with Phosphorus Pentachloride. The oxime mixture (15 mg, 0.10 mmol) and phosphorus pentachloride (110 mg, 0.40 mmol) in ether (5 ml) was stirred for 40 h at room temperature. The mixture was washed with water and dried (Na_2SO_4) and analyzed on GLC (Table II).

Synthesis of 6-*endo*-Cyanobicyclo[3.2.1]oct-2-ene (12) from 6-*endo*-Hydroxymethylbicyclo[3.2.1]oct-2-ene (16). 6-*endo*-Hydroxymethylbicyclo[3.2.1]oct-2-ene (**16**,[11] 1.38 g, 10.0 mmol) was oxidized with the Sarett reagent[26] prepared from chromic anhydride (2.00 g, 20.0 mmol) and pyridine (30 ml) for 100 min at room temperature. The reaction mixture was diluted with ether (100 ml) and the resulting precipitates were removed by filtration. The filtrate was washed with water (20 ml), 10% hydrochloric acid (3 × 20 ml), and 5% aqueous sodium bicarbonate (10 ml) successively, and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded crude aldehyde **15** as an oil (1.0 g, 73%), ir (neat) 2700, 1710, and 1630 cm^{-1}, which was treated with hydroxylamine hydrochloride (2.1 g, 30 mmol) in 95% ethanol (50 ml) containing KOH (3.4 g, 60 mmol) under refluxing for 1 h. The cooled mixture was concentrated to ca. 20 ml, diluted with water (100 ml), and extracted with methylene chloride (3 × 30 ml). The combined extracts were dried (Na_2SO_4) and evaporated to give curde oxime **14** as an oil (0.8 g). Chromatography on a silica gel column eluting with $CHCl_3$–MeOH afforded pure oxime **14** as an oil (0.605 g, 40.0% from **16**): $n^{22}D$ 1.5268; ir (neat) 3260, 3100, 3030, 1640, 1450, 1320, 930, 905, 755, and 710 cm^{-1}; NMR ($CDCl_3$) δ 7.45 and 6.82 (each d, J = 7.0 Hz, 0.6 and 0.4 H, CH=NOH), 6.15–5.25 (m, 3 H, 2 H after shaking with D_2O, OH and CH=CH), 3.65 (d, J = 7.0 Hz, CHCH=NOH), and 3.1–0.9 (m, 8 H, other protons).

Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.36; H, 8.78; N, 8.99.

A mixture of **14** (180 mg, 1.19 mmol) and acetic anhydride (3 ml) was refluxed for 15 h. The cooled mixture was diluted with water (10 ml), stirred for 5 h at room temperature, and extracted with ether (3 × 20 ml). The combined extracts were washed with 5% aqueous sodium bicarbonate (2 × 10 ml) and dried (Na_2SO_4). Evaporation of the solvent gave crude nitrile **12** which on chromatography (silica gel, *n*-hexane) afforded **12** as an oil (110 mg, 69.5%). GLC retention times, nD value, and spectral (ir and NMR) data were identical with those of the sample obtained from the Beckmann fragmentation reaction of **8a**.

Hydrogenation of 12 and 13 to 6-*endo*-Cyanobicyclo[3.2.1]octane (17). Nitrile **12** (30 mg, 0.23 mmol) was hydrogenated in methanol (3 ml) with 10% Pd/C (12 mg) for 5 h under atmospheric pressure at room temperature. After removal of the catalyst by filtration, the methanol solution was evaporated to dryness under reduced pressure to give **17** as colorless crystals, which were purified by sublimation (80 °C, 25 mm) (22 mg, 72.0%): mp 85–88 °C; ir (KBr) 2930, 2860, 2230, and 1460 cm^{-1}; NMR ($CDCl_3$) δ 2.80 (m, 1 H), 2.30 (m, 2 H), and 2.1–0.6 (m, 10 H).

Anal. Calcd for $C_9H_{13}N$: C, 79.95; H, 9.69; N, 10.36. Found: C, 80.23; H, 9.89; N, 10.15.

Nitrile **13** (20 mg, 0.15 mmol) was hydrogenated under similar conditions to afford **17** (15 mg, 74.0%) which was identical with the sample from **12** on the basis of GLC retention times, ir, and NMR spectra.

Fragmentations of Lactam 9 → 11 and of 10 → 12 + 13. Each lactam **9** or **10** was treated with 20 w/w PPE in $CHCl_3$ under reflux for appropriate times, and the products were analyzed on GLC after workup as above. A 41.6:58.4 mixture of **9** and **10** was also treated similarly in order to compare the relative reactivity (see text).

Acknowledgments. We express our appreciation to Professor A. Nickon of the Johns Hopkins University for sending us copies of spectral data and details for preparation of **7**.

Registry No.—**7**, 17931-67-8; **8s**, 58408-37-0; **8a**, 58408-38-1; **9**, 58408-39-2; **10**, 58408-40-5; **11**, 58408-41-6; **12**, 58408-42-7; **13**, 58408-43-8; **14**, 58408-44-9; **15**, 58408-45-0; **16**, 39837-57-5; **17**, 58408-46-1.

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Solvolysis of Benzobicyclo[3.2.1]octenylmethyl Tosylates

Martin Haslanger, Steven Zawacky, and Richard G. Lawton*

Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109

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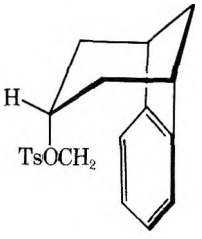
exo- and *endo*-benzobicyclo[3.2.1]octenylmethyl tosylates (1 and 11) were synthesized from the pyrrolidine enamine of 2-indanone using methyl-β,β'-dibromoisobutyrate (3) in an α,α' annelation reaction. The endo hydroxymethyl tosylate 1 undergoes acetolysis at 75 °C with a rate of 2.3×10^{-5} s^{-1}, 58 times that of the exo methyl tosylate (11). The products of the acetolysis of 1 were completely rearranged having a benzobicyclo[3.3.1]nonane skeleton (acetate 13 and olefin 12).

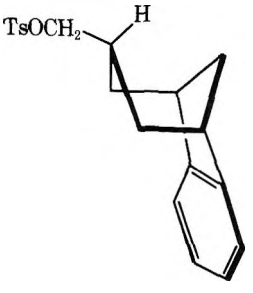
Participation of an aromatic moiety to the site of a developing cation is an area of organic chemistry which continues to be a source of fascinating and informative investigations.[1] Included among those structural factors which affect the contribution of aryl π-participation are the orientation of the aromatic ring with respect to the leaving group, the nature of the substituents on the aromatic ring, and the number and type of bonds in the chain between the aromatic ring and leaving group as well as the number of degrees of freedom in that chain. In spite of many extensive studies, there are few examples of systems in which a remote, developing primary cation is constrained to the face of an aromatic ring.[2] The benzobicyclo[3.2.1]octenyl-*endo*-methyl tosylate structure (1) contains this advantageous characteristic.



1

The synthetic design for a molecule such as 1 in which only a single mode of participation was likely to occur and in which the essential configurational and steric relationships were maintained was facilitated by the demonstrated ability of our α,α' annelation reaction[3] to provide unstable endo stereoisomers in the construction of bicyclic frameworks. Annelation of the pyrrolidine enamine of 2-indanone[4] 2 with β,β'-dibromoisobutyrate 3 yielded crystalline benzobicyclo[3.2.1]octenyl ester 5 by way of the intermediate enamine acrylate 4.[5] The endo stereochemistry of the ester function in bicyclic 5 was supported by its conversion to exo epimer 6 with sodium methoxide–methanol, accompanied by a shift in the ^1H NMR resonance of the ester methyl to lower field. The ester methyl of endo ester 5 lies in the shielding cone of the benzene ring and resonates at 0.5 ppm higher field in the ^1H NMR than the methyl of exo ester 6. Keto ester 5 was converted to its tosylhydrazone and reduced with lithium aluminum hydride.[6] The resulting endo alcohol 7 was characterized as acetate 8. Starting from exo ester 6, an identical route yielded alcohol 9 and acetate 10. The ^1H NMR data of alcohols 7 and 9 and acetates 8 and 10 indicated that the stereochemistry of esters 5 and 6 was maintained during the transformations. The *p*-toluenesulfonates 1 and 11 were prepared from the corresponding alcohols in the usual manner.[7]

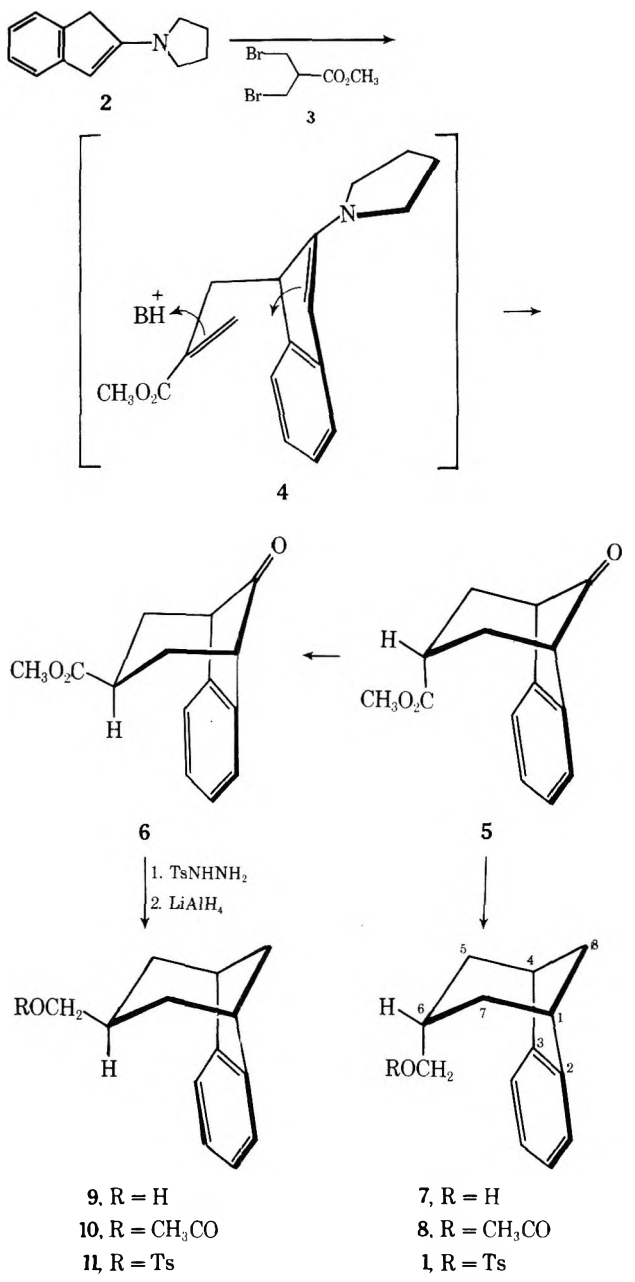
The severe diaxial interactions in the endo methyl tosylate 1 might cause it to have a significant population of the boat conformation 1a, destroying the geometry appropriate for



1a

participation. Such a conformation is developed in the corresponding bicyclo[3.3.1]nonanone methyl derivatives.[3c] Nevertheless both the solvolytic data and ^1H NMR of endo tosylate 1 at room temperature and low temperature suggest that it exists predominantly in the chair form 1. Protons of the methylene bearing the tosylate, in endo epimer 1, occur 1.1 ppm upfield of those in the epimeric exo tosylate 11 and are unchanged to −80 °C in acetone. There is also evidence from lactonization experiments on other members of the benzobicyclo[3.2.1]octenyl series that the chair form is the predominant conformation.[3b]

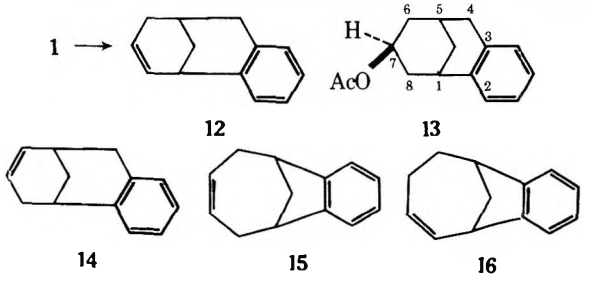
The suitability of the architecture of endo tosylate 1 for participation was reflected by both its enhanced rate and by its products of acetolysis which were completely rearranged. Acetolysis of bicyclic endo methyl tosylate 1 at 75 °C proceeded with a rate of 2.3×10^{-5} s^{-1}, 58 times faster than the corresponding exo methyl tosylate 11 and 100 times faster than isobutyl tosylate.[8] The products of endo methyl tosylate



9, R = H
10, R = CH_3CO
11, R = Ts

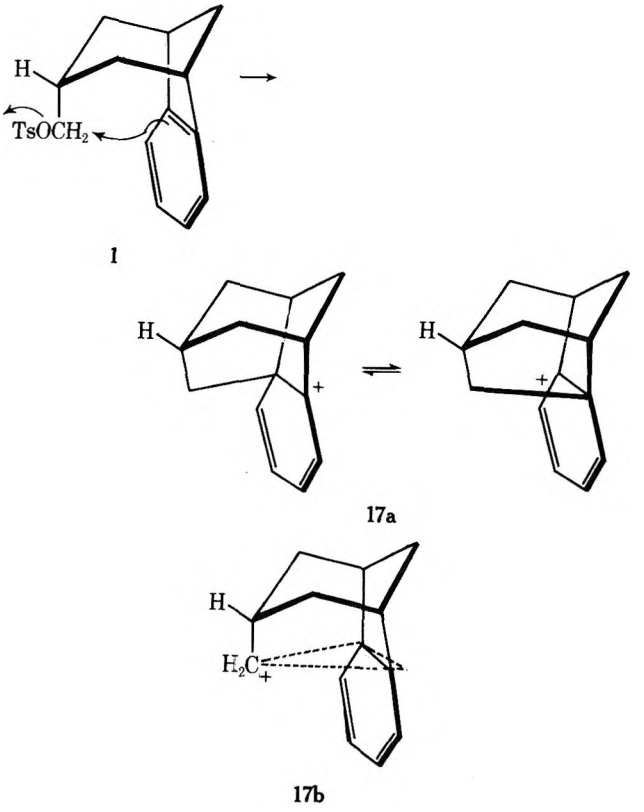
7, R = H
8, R = CH_3CO
1, R = Ts

1 acetolysis were of completely rearranged structure. None of the unrearranged acetate 8 was detected in the solvolysis mixture (limit about 2%) which was composed only of olefin 12 and acetate 13 in a ratio of 3:7.5. The proposed structures



of the solvolysis products are supported by spectral data. Olefin 12 is consistent with its ^1H NMR which showed two vinyl protons, four aromatic, five allylic or benzylic protons, and three aliphatic protons. The observation of three aliphatic protons (δ 2.1–1.7) appeared to eliminate the isomeric olefin 14. This conclusion is in accord with reported NMR data for bicyclo[3.3.1]nona-2,6-diene.[9] Similar arguments rule out olefins 15 and 16. Both the VPC behavior and single acetate methyl at δ 1.93 suggested the formation of only one epimer at carbon 7 for 13 and the stereochemistry of the acetate follows from mechanistic considerations as well as its NMR.

A mechanism consistent with these results is ionization of tosylate 1 with concomitant formation of species 17a and/or 17b.



Because the position of the developing cation above the aromatic ring is fixed directly between the two participating carbons in 1, the contribution of form such as 17b as an intermediate may be enhanced over that of 17a. Such symmetry as in 1 may require a somewhat different mode of participation than that required for Ar_1-5 or Ar_2-6[10] participation alone.

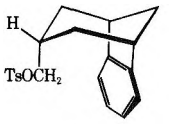
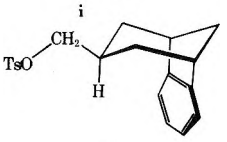
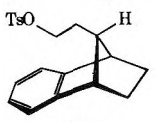
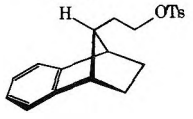
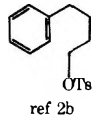
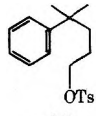
The stabilized ion 17 could have taken several routes to restore the aromaticity of the participating phenyl nucleus. Elimination of axial hydrogens at carbons 6 or 8 could yield olefins 12 and/or 14. The reason for the formation of only olefin 12 is not apparent.

Alternatively, the ion 17 could be attacked directly by an acetate nucleophile at carbons 4 or 7. Absence of acetate 8 in the solvolysis mixture ruled out any observable attack at carbon 4. Exclusive rearrangement of the bridged ion 17 is consistent with the labeling experiments of Jackman and co-workers.[11] Acetate attack at carbon 7 of ion 17 should lead to the exo stereochemistry proposed for acetate 13.

The rate of acetolysis of endo tosylate 1 also supports the presence of participation in the rate-determining ionization process. The acetolysis of exo tosylate 11, which gives only the nucleophilic displacement product, acetate 10, proceeds at a much slower rate. Absolute and relative rates of acetolysis of this and other relevant aryl tosylates are accumulated in Table I. While consistent with the rate observed for a simple model, isobutyl tosylate, the solvolysis rate of exo tosylate 11 is probably not an ideal comparison rate for the endo tosylate 1 because of the greater distance of the function from the aromatic ring. While the steric environment of the endo tosylate 1 is such that solvolytic displacement by acetate is severely impeded if not impossible, the rate observed for 11 is likely due only to displacement.

A rearrangement–internal return pathway followed by a slower acetolysis of the rearranged sulfonate was not signifi-

Table I. Rates of Acetolysis at 75 °C

X = OTs	s^{-1}	Relative	k_{endo}/k_{exo}
	2.3×10^{-5}	100	Δ 58
i 	4×10^{-7}	1.7	
ii  ref 2a	7.3×10^{-6}	32	Δ 9.7
 ref 2a	7.7×10^{-7}	3.3	
 ref 2b	4.8×10^{-7}	2	
 ref 2c	6.3×10^{-7}	2.7	
 ref 8	2.3×10^{-7}	1	

cantly affecting the rate of acetolysis of compound **1**. The acetolysis rate could be easily monitored by NMR using perdeuterioacetic acid solvent at 59 °C. Comparison of the rate of appearance of the methyl signal of *p*-toluenesulfonic acid (δ 2.4), the rate of formation of the distinctive signal for the aromatic portions of **12** and **13** (δ 7.1), and the rate of disappearance of both the methyl signal of the *p*-toluenesulfonate (δ 2.5) and the aromatic singlet (δ 6.9) of starting tosylate **1** proved the concomitant rearrangement and solvolysis. The rate obtained by this study was comparable to that obtained by titration at the higher temperature (about 8×10^{-6} s^{-1} at 58 °C).

Though the difference in relative rates between **1** and **11** is not highly dramatic (endo/exo rate ratio of 59) compared with double bond rate ratios, this example gives some suggestion of the maximum rate expected in primary carbon participation of aromatics without activating substituents. The previous maximum rate ratio for aromatic participation was observed by Tanida and Muneyuki[2] having a participation rate ratio of 9.7 (endo/exo) (Table I). Their example, having an ethyl side chain, has more degrees of freedom.

Experimental Section

General. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton magnetic resonance spectra were obtained on Varian Associates T-60 and T-60A instruments and a JEOL JNM PS-100 spectrometer. Mass spectra were obtained on an Associated Electrical Industries MS-902. Infrared spectra were recorded on a Perkin-Elmer 457 spectrophotometer. Vapor-phase chromatography was performed on a Varian Aerograph Model 90-P3 instrument using the following columns: A, 5% SE-30 on Chromosorb G, 0.25 in. × 6 ft; B, 5% SE-30 Chromosorb G, 0.25 in. × 1.5 ft. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Spectral data were obtained as follows: NMR as solutions in deuteriochloroform (units in parts per million downfield from internal Me_4Si); ir as solutions in chloroform or deuteriochloroform (units in cm^{-1}, calibrated with the 1601-cm^{-1} polystyrene absorbance); *m/e* 70 eV.

Methyl Benzobicyclo[3.2.1]octen-8-one-3-*endo*-carboxylate (5). To a solution of 27.7 g (0.150 mmol) of the pyrrolidine enamine of 2-indanone **2** and 30.4 g (0.30 mmol) of triethylamine in dry methanol (300 ml) was added 39.0 g (0.15 mmol) of methyl β,β′-dibromoisobutyrate over a 10-min period. The resulting solution was heated to reflux under nitrogen for 3 h, water (75 ml) added, and the mixture allowed to cool to ambient temperature for 2 h. Water (225 ml) was then added to the reaction mixture and the resulting solution extracted with chloroform (5 × 100 ml). The combined chloroform extracts were washed with 10% HCl (2 × 300 ml), saturated $KHCO_3$ (2 × 250 ml), and saturated NaCl (2 × 250 ml) and dried (Na_2SO_4). The solvent was removed to yield a dark oil which was taken up in chloroform and filtered through alumina, and the resulting solution taken to dryness. The material obtained from the alumina filtration was sublimed (100–107 °C at 0.1 mm) to yield 9.7 g (28%) of the benzobicyclo[3.2.1]cyclooctenyl ester **5**: mp 106–108 °C; ir 1720, 1760 cm^{-1}; NMR δ 3.6 (s, 3 H, OCH_3), 7.25 (s, 4 H, Ph); *m/e* 230.

Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 73.14; H, 6.16.

Methyl Benzobicyclo[3.2.1]octen-8-one-3-*exo*-carboxylate (6). To a solution of 3 mmol of sodium methoxide in methanol (12 ml) was added 690 mg (3 mmol) of the endo ester **5**. The solution was heated to reflux under nitrogen for 34 h. The cooled reaction mixture was acidified with 5% acetic acid and the resulting solution was extracted with methylene chloride (30 ml). The methylene chloride solution was washed with 5% $KHCO_3$ (10 ml) and dried (Na_2SO_4). The solvent was removed to yield 547 mg (79%) of the exo ester **6**: mp 105–108 °C; ir 1760, 1725 cm^{-1}; NMR δ 3.64 (s, 3 H, OCH_3), 7.25 (s, 4 H, Ph); *m/e* 230.

Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 73.14; H, 6.16.

Benzobicyclo[3.2.1]octenyl-*endo*-methyl Alcohol (7). To a solution of 920 mg (4 mmol) of the endo ester **5** in tetrahydrofuran (THF) (10 ml) was added 800 mg (4.3 mmol) of *p*-toluenesulfonylhydrazine and 5 drops of acetic acid. The solution was allowed to stand at ambient temperature for 25 h, then the solvent was removed and the tosylhydrazone dried in vacuo to give a white solid foam which showed no ketone absorbance (1760 cm^{-1}) in the ir. To a slurry of $LiAlH_4$ (600 mg) in dry THF was added a solution of the tosylhydrazone in THF (15 ml). The resulting mixture was heated to reflux under nitrogen for 24 h, an additional 100 mg of $LiAlH_4$ added, and the reflux continued for 58 h. The excess hydride was quenched by the addition of ethyl acetate followed by saturated NH_4Cl (10 ml) and the resulting solution stirred at ambient temperature for 0.5 h. The granular precipitate was filtered and washed with methylene chloride (50 ml) and ether (40 ml). The combined organic solutions were washed with 2 N HCl (50 ml), saturated $KHCO_3$ (50 ml), and saturated NaCl (40 ml) and dried (Na_2SO_4). The solvent was removed to yield 460 mg (65%) of the crude alcohol **7** as an oil: ir 3590, 2920 cm^{-1}; NMR δ 2.2 (m, 2 H), 3.1 (m, 2 H), 7.11 (s, 4 H, Ph); *m/e* 188. Attempted preparation of an analytical sample of the alcohol by VPC failed, apparently owing to decomposition. An acceptable analysis was obtained on the acetate derivative **8**.

Benzobicyclo[3.2.1]octenyl-*exo*-methyl Alcohol (9). To a solution of 890 mg (3.9 mmol) of the exo keto ester **6** in tetrahydrofuran (THF) (10 ml) was added 745 mg (4.0 mmol) of *p*-toluenesulfonylhydrazine and 5 drops of acetic acid. The resulting solution was allowed to stand at ambient temperature for 24 h, then the solvent was removed and the tosylhydrazone dried in vacuo. To a slurry of 800 mg of $LiAlH_4$ in dry THF was added a solution of the tosylhydrazone in THF (10 ml). The resulting mixture was heated to reflux, under nitrogen, for 44 h, an additional 200 mg of $LiAlH_4$ added, and the reflux continued for 84 h. The reaction mixture was processed as in the preparation of alcohol **7** to yield 658 mg (90%) of the exo methyl alcohol **9** as an oil: ir 3590, 2920 cm^{-1}; NMR δ 3.39 (d, 2 H), 7.18 (s, 4 H, Ph); *m/e* 188. Again attempted preparation of an analytical sample by VPC failed, apparently owing to decomposition of the alcohol. An acceptable analysis was obtained for the acetate derivative **10**.

Benzobicyclo[2.1.1]octenyl-3-*endo*-methyl Tosylate (1). To an ice-cooled solution of 500 mg (2.7 mmol) of endo alcohol **7** in dry pyridine (7.5 ml) was added 1.02 g (5.3 mmol) of *p*-toluenesulfonyl chloride. An immediate color change was noted as a reddish-yellow color appeared. The solution, in a stoppered Erlenmeyer flask, was allowed to stand in a refrigerator for 210 h. The reaction mixture was poured into 30 ml of ice water and the mixture was stirred until the

ice melted. The aqueous mixture was extracted with ether (75, 25 ml) and the combined ether extracts were washed with cold 2 N HCl (2 × 30 ml), water (20 ml), and saturated NaCl (20 ml) and dried (Na_2SO_4). The solvent was removed to yield 821 mg (90%) of the crude tosylate **1**. The tosylate was recrystallized from pentane–ether: mp 59–61 °C; ir 1175, 1190 cm^{-1}; NMR δ 2.43 (s, 3 H), 6.98 (s, 4 H, Ph); *m/e* 342.

Anal. Calcd for $C_{20}H_{22}O_3S$: C, 70.08; H, 6.47. Found: C, 69.78; H, 6.16.

Benzobicyclo[3.2.1]octenyl-3-*exo*-methyl Tosylate (11). To an ice-cooled solution of 323 mg (1.7 mmol) of exo alcohol **9** in dry pyridine (5 ml) was added 665 mg (3.5 mmol) of *p*-toluenesulfonyl chloride. An immediate color change occurred and a bright yellow color was noted. The resulting mixture was processed as in the preparation of the endo tosylate **1** to give 525 mg (90%) of crude exo tosylate **11** which was purified by recrystallization from pentane–ether: mp 60–62 °C; ir 1175, 1190 cm^{-1}; NMR δ 2.42 (s, 3 H, CH_3), 3.13 (m, 2 H), 3.77 (d, 2 H, CH_2O–), 7.10 (s, 4 H, Ph); *m/e* 342.

Anal. Calcd for $C_{20}H_{22}O_3S$: C, 70.08; H, 6.47. Found: C, 69.80; H, 6.36.

Acetate Derivative (8) of Endo Alcohol 7. To a solution of 100 mg of endo alcohol **7** in acetic anhydride (2 ml) was added 10 drops of pyridine and the resulting solution heated to 70 °C under nitrogen for 18 h. The reaction mixture was poured into water (25 ml) and the resulting aqueous solution was extracted with ether (30 ml). The ether extract was washed with 2 N HCl (20 ml), saturated $KHCO_3$ (20 ml), and saturated NaCl (15 ml) and dried (Na_2SO_4). The solvent was removed to yield 118 mg of acetate **8** as an oil. An analytical sample was obtained by preparative VPC on column A: ir 170 cm^{-1}; NMR δ 1.90 (s, 3 H, CH_3CO–), 2.75 (d, 2 H), 3.10 (m, 2 H), 7.17 (s, 4 H); *m/e* 230.

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.83. Found: C, 78.40; H, 7.83.

Acetate Derivative (10) of Exo Alcohol 9. To a solution of 100 mg of alcohol **10** in acetic anhydride (2 ml) was added 10 drops of pyridine and the resulting solution was heated to 80 °C under nitrogen for 14 h. The reaction mixture was processed as in the preparation of acetate **8** to yield 45 mg of the exo acetate **10** as an oil. An analytical sample was obtained by preparative VPC on column A: ir 1715 cm^{-1}; NMR δ 1.93 (s, 3 H, CH_3CO), 3.10 (m, 2 H), 3.80 (d, 2 H, CH_2O–), 7.10 (s, 4 H, Ph); *m/e* 230.

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.83. Found: C, 78.19; H, 7.86.

Acetolysis of Endo Tosylate 1. A solution of 105 mg (0.3 mmol) of tosylate **1** in glacial acetic acid (1.4 ml) was sealed in a ampule and heated at 75 °C for 12 h. The cooled reaction mixture was poured into water (10 ml) and methylene chloride (20 ml). The organic phase was washed with saturated $KHCO_3$ (10 ml) and saturated NaCl (10 ml) and dried (Na_2SO_4). The solvent was removed to yield 81 mg of a crude oil which was a mixture of acetate **13** and olefin **12** in the approximate ratio 7.5:3 (determined by VPC) and also contained some unreacted tosylate **1** (NMR). Analytical samples were obtained by preparative VPC on columns A and B.

Acetate **4**: ir 1720 cm^{-1}; NMR δ 1.93 (s, 3 H, CH_3CO), 4.93 (m, 1 H, HCO–); *m/e* 230.

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.83. Found: C, 78.53; H, 7.96.

Olefin **3**: ir 3015 cm^{-1}; NMR δ 5.67 (m, 2 H, HC=CH), 7.07 (s, 4 H, Ph); *m/e* 170.

Anal. Calcd for $C_{13}H_{14}$: C, 91.71; H, 8.29. Found: C, 91.55; H, 8.45.

Acetolysis of Endo Tosylate 1 in Deuterioacetic Acid. A 30-mg sample of tosylate **1** was dissolved in 0.5 ml of deuteroacetic acid in an NMR tube. Immediate scan of the mixture at the temperature of the probe (35 °C) showed no new peaks. Scans at 10, 20, and 40 min showed no changes. After 12 h the spectrum remained essentially unchanged. The NMR tube was then heated in a refluxing chloroform bath. The tube was withdrawn from the bath at intervals and quenched in ice water. The spectrum scan showed the development of the *p*-toluenesulfonic acid methyl singlet at 2.40 ppm and the disappearance of the methyl singlet of **1** at 2.5 ppm. The aromatic signal of **1** at δ 6.95 disappeared and the characteristic multiplet observed for the benzobicyclo[3.3.1]nonane system appeared. At the same time the multiplet for the unshielded O–CH hydrogen of the [3.3.1] system appeared at δ 4.8. Crude rate measurements indicated a $t_{1/2}$ of about 1400–1500 min for each of these processes which compares with the titrimetric rate. VPC of the final mixture showed both olefin **12** and acetate **13**.

Acetolysis of Exo Tosylate 11. A 0.03 M solution of exo tosylate **11** in glacial acetic acid was heated at 75.0 °C to 50% completion. The reaction mixture was processed as in the acetolysis of endo tosylate **1**. The material isolated was identical by NMR and VPC with a mixture of exo tosylate **11** and exo acetate **10**.

Rate Measurements. The procedure used for determination of solvolysis rates is that of Winstein.[12] Aliquots of a 0.032 M solution of endo tosylate **1** in glacial acetic acid, containing 1% by weight acetic anhydride, were sealed in ampules and placed in an oil bath thermostatted at 75.0 °C (±0.1 °C) Ampules were removed at appropriate intervals and immersed in ice. The ampule was then allowed to warm to room temperature and a 5.0-ml aliquot removed and titrated with 0.05 M sodium acetate to a bromophenol blue end point. The rate was followed to ~85% completion and the plot of log (C_0/C_t) vs. time was computed. A regression analysis of the ln (C_0/C_t) as a function of time yielded the rate, $k = 2.28\ (\pm 0.07) \times 10^{-5}\ s^{-1}$.

The identical procedure was used for the exo tosylate **11**. The plot of log (C_0/C_t) against time followed by a regression analysis of ln (C_0/C_t) as a function of time gave the rate, $k = 4.0\ (\pm 0.3) \times 10^{-7}\ s^{-1}$.

Registry No.—**1**, 58426-32-7; **2**, 39157-79-4; **3**, 22262-60-8; **5**, 55529-62-9; **6**, 55511-69-8; **7**, 58426-33-8; **8**, 58426-34-9; **9**, 58462-39-8; **10**, 58462-40-1; **11**, 58462-41-2; **12**, 58426-35-0; **13**, 58426-36-1; sodium methoxide, 124-41-4; *p*-toluenesulfonylhydrazine, 1576-35-8; *p*-toluenesulfonyl chloride, 98-59-9; acetic anhydride, 108-24-7.

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Nonbenzenoid Aromatic Systems. XII.[1a] Synthesis of 2-, 3-, and 6-Substituted 2-(1-Azulyl)ethanols and Their Tosylate Esters

Richard N. McDonald,* James M. Richmond, James R. Curtis,[1b] Herbert E. Petty,[1c] and Thomas L. Hoskins[1d]

Department of Chemistry, Kansas State University, Manhattan, Kansas 66506

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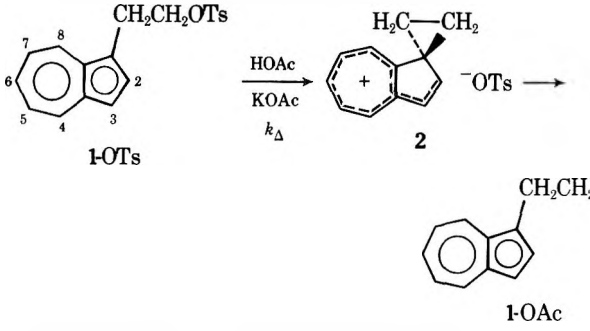
The synthesis of 2- (CH_3O, CH_3, Cl, Br, I, CN) and 3-substituted (CH_3O, CH_3, CH_3S, Br, $COCH_3$, CN, NO_2) derivatives of 2-(1-azulyl)ethanol (1-OH) and 1-OAc by combining conventional procedures are reported. A method for the protodeamination of diethyl 2-amino-6-bromoazulene-1,3-dicarboxylate (3) to diethyl 6-bromoazulene-1,3-dicarboxylate (7) in 93% yield using *p*-hydroquinone as in situ reducing agent of the intermediate diazonium salt is described. 7 and diethyl 6-methoxyazulene-1,3-dicarboxylate were found to hydrolyze when dissolved in concentrated sulfuric acid and then the yellow solution poured into water in excellent yields. The resulting 1,3-diacids were then thermally decarboxylated to 6-bromo- (16) and 6-methoxyazulene (17), respectively. Direct β-hydroxyethylation (ethylene oxide and $AlCl_3$) of 16, 17, and 6-methylazulene gave the respective 6-X-1-OH's. 6-CN-1-OH was prepared from the reaction of 6-Br-1-OAc and cuprous cyanide in DMF followed by hydrolysis. The tosylate esters of these derivatives of 1-OH were generally prepared in ether with powdered potassium hydroxide and *p*-toluenesulfonyl chloride. The substituent effects on λ_{max} of azulene in the visible spectra of the above derivatives are discussed.

In 1971 we reported certain preliminary results on the buffered acetolysis of 2-(1-azulyl)ethyl tosylate (1-OTs) demonstrating that the 1-azulyl substituent was a "superparticipator" in β-arylethyl arenesulfonate solvolyses[2] with $k_{1\text{-OTs}}/k_{PhCH_2CH_2OTs} \sim 10^5$ for the k_Δ process at 25 °C.[3] Buffered acetolysis of 1-OTs was shown to proceed exclusively by the k_Δ process in the absence of ion-pair return and with the ionization step, k_Δ, being rate determining.[3]

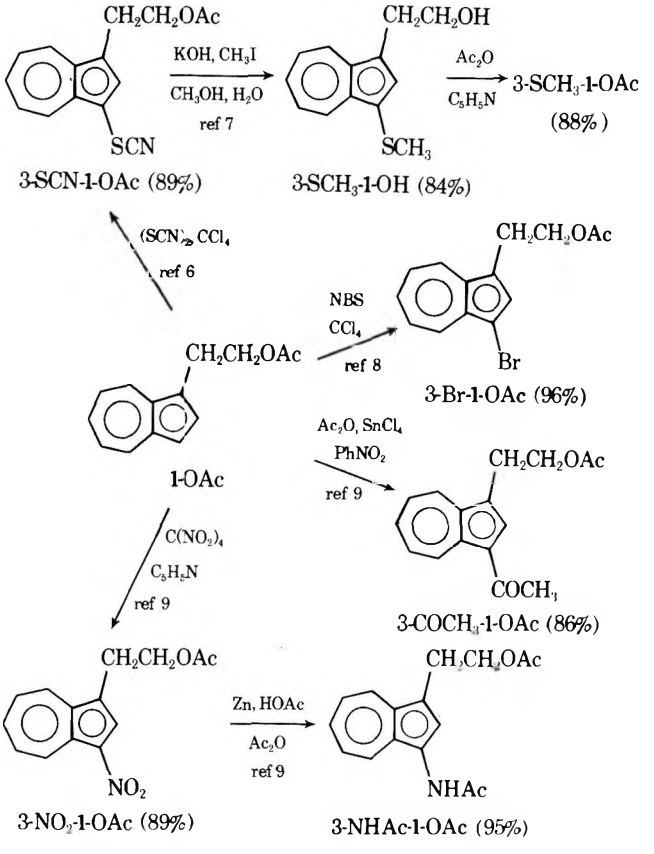


With these primary points established, it became of interest to us to consider how substituents at the seven nonequivalent ring positions in 1-OTs and 2 would influence this k_Δ process. Before such studies could be carried out, appropriate synthetic procedures leading to the desired derivatives must, of course, be developed. It is the syntheses of derivatives of 1-OH at the three most diverse positions, the 2 (benzene ortholike), the 3 (benzene metalike), and the 6 position (long-range benzene paralike), that we wish to describe here.

Two methods are available for introducing the β-ethanol side chain onto the azulene 1 position. The first is the method of Anderson,[4] which involves electrophilic N,N-dimethylaminomethylation, quaternerization with CH_3I, displacement with CN (→ $-CH_2CN$), hydrolysis (→ $-CH_2CO_2H$), and diborane reduction to 1-OH. This was the procedure used in our initial studies, and is most convenient for specific C_α–D_2 labeling with B_2D_6 reduction of 1-azulylacetic acid. The second method involves direct β-hydroxyethylation of azulenes with ethylene oxide and $AlCl_3$[5] and was the method of choice in our later syntheses.

Synthesis of 3-Substituted 1-OH's. The pioneering research of Anderson and his co-workers at the University of Washington in the 1950's and 1960's established the ease and generality of electrophilic substitution at the 1(3) position of azulene and various substituted derivatives. With

Scheme I



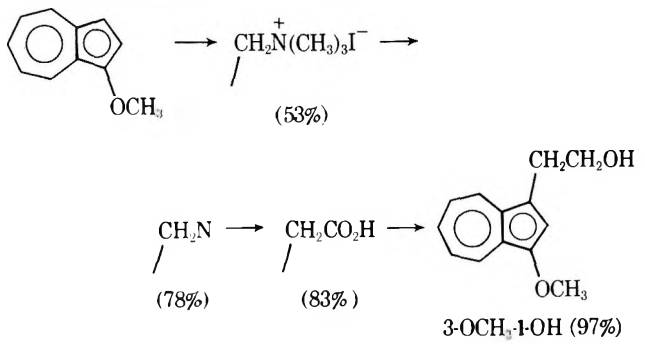
quantities of 1-OH and 1-OAc available by either of the above procedures, the range of desired 3-X-1-OH's (or acetates) was prepared by established methods outlined in Scheme I. Use of the mild nitrating reagent tetranitromethane in pyridine[9] also allowed for direct nitration of 1-OH to 3-NO_2-1-OH in 92% yield.

3-CN-1-OAc was prepared in 32% yield by allowing 3-Br-1-OAc to react with cuprous cyanide in refluxing dimethylformamide (DMF). Direct cyanation of 1-OAc with cyanogen bromide and stannic chloride[10] gave 3-CN-1-OAc in 19% yield.

3-CH_3-1-OH was prepared by N,N-dimethylaminomethylation[4] of 1-OH followed by quaternization of the tertiary

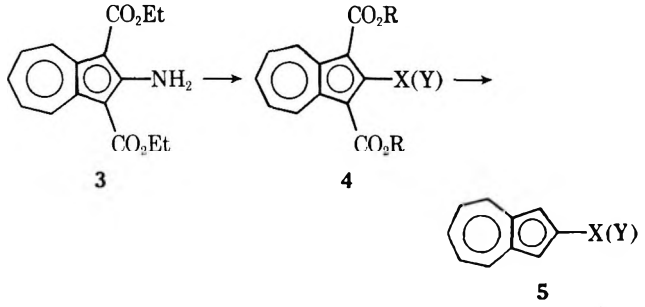
amine with methyl iodide; the yield of the iodide salt was 87%. Reduction of this quaternary salt with sodium borohydride in ethanol under reflux for 7 min gave a 51% yield of 3-CH_3-1-OH which was unstable in the presence of traces of acids. Direct β-hydroxyethylation[5] of 1-methylazulene produced only decomposition.

The synthesis of 3-OCH_3-1-OH starts with 1-methoxyazulene[11] and uses Anderson's stepwise construction of the β-ethanol side chain[4] as shown below. Here also, direct β-hydroxyethylation[5] gave only decomposition.



The 3-X-1-OH or 3-X-1-OAc derivatives thus available are X = CH_3O, CH_3, H, SCH_3, Br, $COCH_3$, CN, and NO_2.

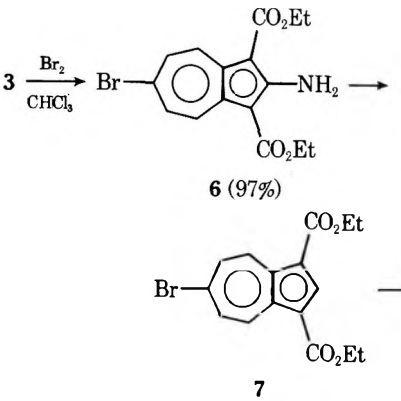
Synthesis of 2-Substituted 1-OH's. The preparation of 2-substituted 1-OH's (also 6-X-1-OH's) utilized the elegant Nozoe azulene synthesis where a substantial number of 2-substituted azulenes have been reported.[1a,12] This synthesis of 2-X-1-OH's begins with diethyl 2-aminoazulene-1,3-dicarboxylate (**3**) and makes use of four factors: (a) replacement of the amino function by X = Cl, Br, or I (**3** → **4**-X),[12] (b) the ease of nucleophilic displacement of X:⁻ by Y:⁻ in **4**,[1a,12] (c) the ability to thermally decarboxylate the azulene-1,3-dicarboxylic acids to the corresponding azulenes,[1,12,13] and (d) the ability of **5** to undergo halogen interchange [**5** (X = Cl) → **5** (X = I)]. Thus we had available



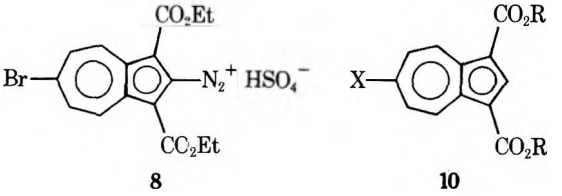
2-substituted azulenes (**5**) where X = CH_3O, CH_3, Cl, Br,[14] and I.[12] Each of these was β-hydroxyethylated (direct method)[5] in high net yield to the respective 2-X-1-OH which were purified by repeated chromatography or (better) by conversion to the 2-X-1-OAc, purification, and hydrolysis to the alcohols. 2-CN-1-OH was prepared by treating 2-I-1-OAc in refluxing DMF with cuprous cyanide in 86% yield followed by hydrolysis to the alcohol.

Thus, the 2-X-1-OH derivatives available are X = CH_3O, CH_3, H, Cl, Br, I, and CN.

Synthesis of 6-Substituted 1-OH's. As pointed out above, the preparation of 6-X-1-OH's also began with amino diester **3** in the Nozoe synthesis. The preparation of this series of compounds was made possible by Nozoe's finding that (a) bromination of **3** proceeds exclusively to diethyl 2-amino-6-bromoazulene-1,3-dicarboxylate (**6**)[12a] and (b) nucleophiles readily replace Br in diethyl 6-bromoazulene-1,3-dicarboxylate (**7**),[15] and our discoveries of (c) the essentially quantitative hydrolysis of dialkyl azulene-1,3-dicarboxylates to their diacids when the esters were dissolved in concentrated sulfuric acid and quenched in water,[16] and (d) a superior method for the protodeamination of **6** → **7**.[17]



Since bromo diester **7** appeared to be the key compound in the synthesis of a variety of 6-substituted azulenes, efforts were made to optimize the protodeamination of **6**. In a modification of Nozoe's procedure,[15] amine **6** was converted to the purple-blue diazonium salt **8** in dioxane with sulfuric acid and sodium nitrite, the latter dissolved in a small amount of water. Addition of a premixed solution of sulfuric acid and sodium hypophosphite in water gave a 50% yield of **7**. When the diazotization reaction was carried out in the presence of finely ground, suspended sodium hypophosphite a 1:1 mixture of **7** and diethyl 2,6-dibromoazulene-1,3-dicarboxylate (**9**) was isolated. Reduction of **8** with



sodium borohydride[18] gave **7** and **9** in a 1:9 ratio. Use of ethanol as solvent and reducing agent in the diazotization of **6** gave a 26% yield of **7**.

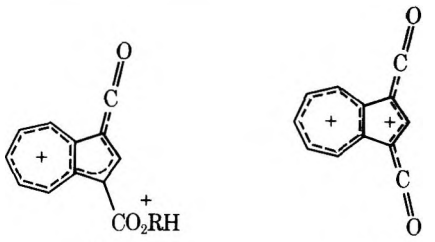
At least two factors contributed to the poor yields of **7**: (1) inefficiency in the reduction of **8** to **7**, and (2) competitive formation of Br^- and attack by this nucleophile at C_2 of **8** leading to dibromide **9**. The susceptibility of the C_6–Br bond of **8** toward nucleophilic displacement has been reported recently by Nozoe.[19]

Our search for a better protodeamination process for the **6** → **7** conversion thus centered on finding conditions involving an in situ reducing agent to be used in a nonaqueous, nonnucleophilic solvent. Orton and Everatt[20a] in 1908 mentioned that *p*-hydroquinone (H_2Q) reduced aryldiazonium salts. We found the H_2Q proved most suitable as the in situ reducing agent in dioxane solvent with isopentyl nitrite and sulfuric acid generating the nitrosating reagent.[17] Since the amine and H_2Q compete for the nitrosating reagent, excesses of H_2Q and alkyl nitrite are required in this in situ protodeamination method. *The yield of purified* **7** *from* **6** *was 93%*. The high efficiency of this protodeamination is also seen in the fact that the deep purple-blue color of intermediate **8** is *not* observed in this reaction. The present procedure[21] should prove to be the method of choice especially where unstable, highly reactive aryldiazonium salts are produced and/or expensive amines are involved.

With bromo diester **7** now available it was possible to proceed to the next step in the synthesis of 6-X-1-OH's. At this point, the ease of displacing Br^- from **7** by various nucleophiles, which was useful in preparing a number of derivatives of diester **10** (R = Et), became a problem when it

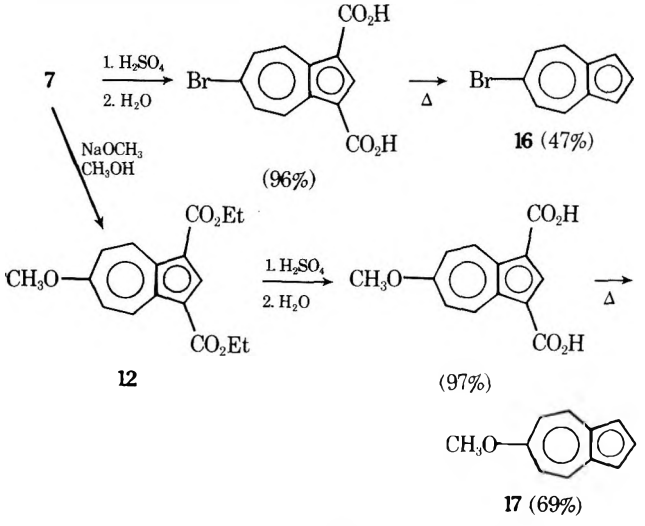
came time to remove the 1,3-dicarboethoxy groups to obtain the desired 6-X-azulenes. Nozoe had reported that "mild alkaline treatment of" **7** produced diethyl 6-hydroxyazulene-1,3-dicarboxylate (**11**);[15] this was readily verified in our work. With **7** and sodium methoxide in methanol, diethyl 6-methoxyazulene-1,3-dicarboxylate (**12**) was formed in 82% yield; Nozoe had prepared the ethyl ether of **12** in an analogous reaction.[15] When we attempted to saponify **12**, the first reaction to occur was formation of the conjugate base of **11**.[22] It was obvious at this point that acid hydrolysis conditions would be needed for the conversion of **7** and **12** to their corresponding diacids which might then be decarboxylated to yield 6-bromo- (**16**) and 6-methoxyazulene (**17**), respectively.

Considering the structure of diethyl azulene-1,3-dicarboxylate (**13**) and recalling the classic results of Treffers and Hammett[23] in the esterification–hydrolysis of mesitoic acid and its esters via the acylium ion produced in sulfuric acid, it appeared reasonable that **13** could yield mono- (**14**) and diacylium ions (**15**) in strong acid. When **7** and **12** were



14 **15**

dissolved in concentrated sulfuric acid and these solutions then poured into ice–water, nearly quantitative yields of the corresponding diacids were obtained. Each diacid was then thermally decarboxylated to the respective 6-substituted azulene. When **7** or **13** was dissolved in concentrated sulfuric acid in an NMR tube, the hydrolysis could be followed by NMR spectroscopy. However, only the absorptions of the conjugate acids of the starting esters, intermediate half-esters, and product diacids were observed; 6-Br-**14** and 6-Br-**15** had been observed previously in SbF_5–FSO_3H–SO_2.[16] The 2–3% water in reagent concentrated sulfuric acid was probably responsible for the different observations in the two media.

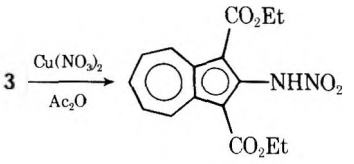


16 and **17** were β-hydroxyethylated (direct)[5] to give the desired 6-Br-1-OH and 6-OCH_3-1-OH in 41% (90% net) and 48% (93% net) yields, respectively. An attempt to carry out Anderson's stepwise β-hydroxyethylation[4] with **16** led to decomposition during the base hydrolysis of 6-bromo-1-azulylacetonitrile.

When **7** was allowed to react with potassium cyanide in ethanol, the sole product isolated was diethyl 6-ethoxyazulene-1,3-dicarboxylate, previously prepared by Nozoe from the reaction of **7** and sodium ethoxide in ethanol.[15] Replacement of Br^- (in **7**) by ^-CN was accomplished with cuprous cyanide in DMF at 130 °C giving a 50% yield of diethyl 6-cyanoazulene-1,3-dicarboxylate (**18**) along with an 18% yield of diethyl 6-dimethylaminoazulene-1,3-dicarboxylate (**19**).[15] Amine diester **19** must have resulted from partial hydrolysis of the solvent DMF. The chemistry of **18** was not further explored.

6-Cyanoazulene (**20**) was obtained from the reaction of **16** with cuprous cyanide in DMF in 78% yield. As expected, **20** failed to undergo direct β-hydroxyethylation with 70% of **20** being recovered from the reaction. However, 6-CN-1-OAc was obtained from the reaction of 6-Br-1-OAc with cuprous cyanide in DMF. Base hydrolysis of 6-CN-1-OAc produced 6-CN-1-OH.

Since bromination of **3** had proceeded smoothly to yield **6** which ultimately was converted into 6-Br-1-OH, a successful nitration of **3** could conceivably produce 6-NO_2-1-OH. While tetranitromethane in pyridine[9] gave no reaction with **3**, the reaction of **3** and cupric nitrate in acetic anhydride[6,8a,9] produced a base-soluble product. Elemental and spectral analysis of this acidic compound established that it was not the expected C-nitration product, 6-NO_2-**3**, but rather the isomeric product of N-nitration, diethyl 2-nitroaminoazulene-1,3-dicarboxylate (**21**).



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We[24] had previously prepared 6-methylazulene by a modification of the Ziegler–Hafner azulene synthesis.[25] Direct β-hydroxyethylation[5] of 6-methylazulene gave 6-CH_3-1-OH along with a small amount of 2,2′-(6-methyl-1,3-azulene)diethanol, the latter structure assigned on the basis of its NMR spectrum.

The 6-X-1-OH (or acetate) derivatives prepared in this study were X = CH_3O, CH_3, H, Br, and CN.

Preparation of the Tosylate Esters. In general, the tosylate esters of the above derivatives of 1-OH were prepared by treating the alcohol in ether at 0 °C with freshly sublimed *p*-toluenesulfonyl chloride and crushed potassium hydroxide.[26] It was believed that this procedure would "ensure" the structural integrity of certain of the more reactive substrates during this derivatization. Certain of the tosylates were oily liquids and were routinely converted to their *sym*-trinitrobenzene (TNB) complexes for analysis and storage; in several cases, the TNB complexes were stable to storage for months in the refrigerator while the uncomplexed, liquid tosylates decomposed after short periods of time.

Substituent Effects on λ_{max} in the Visible Region of Azulenes. While the major emphasis of this synthetic work was to prepare substituted 2-(1-azulyl)ethyl tosylates for solvolytic studies, it is of interest to observe the substituent effects on the λ_{max} in the visible spectra of these azulene derivatives. We have a number of various types of substituents on the azulene ring 2, 3, and 6 positions, and their shifts ($\Delta\lambda_{max}$) as well as those of the related monosubstituted azulenes are listed in Table I.

The small changes in λ_{max} seen in going from 1-OH (596 nm) to 1-OAc (593 nm) to 1-OTs (590 nm) in CH_2Cl_2 solvent appear to be real since the same trend is noted in all

Table I. Comparison of Substituent Effects on the Visible λ_{max} of 1-OH, 1-OAc, and 1-OTs and Related Monosubstituted Azulenes

	$\Delta\lambda_{max}$, nm[a,i]		$\Delta\lambda_{max}$, nm[b]	Ref
2-CH_3O-1	−60 ± 1 (3)[c]	2-CH_3O-Az	−57	*i*, 12a
2-CH_3-1	−18 ± 2 (2)	2-CH_3-Az	−18[g]	*i*
2-Cl-1	−30 ± 2 (2)	2-Cl-Az	−29	*j*, 12a
2-Br-1	−28 ± 1 (3)	2-Br-Az	−23	*i*
2-I-1	−18 (1)[d,e]	2-I-Az	−20	*j*, 12a
2-NC-1	53 ± 2 (3)	2-NC-Az	55	12a
3-CH_3O-1	101 ± 2 (2)	1-CH_3O-Az	104	*i*, 11
3-CH_3-1	29 ± 1 (2)	1-CH_3-Az	28	4
3-CH_3S-1	22 ± 1 (2)	1-CH_3S-Az	1	7
3-Br-1	17 ± 2 (2)	1-Br-Az	25	8a
3-NCS-1	−20 ± (1)[d,f]	1-NCS-Az	−27[h]	6
3-CH_3CO-1	−38 ± 1 (2)	1-CH_3CO-Az	−30	8a
3-NC-1	−34 (1)	1-NCAz	−24	*k*, *l*
3-O_2N-1	−65 ± 2 (3)	1-O_2N-Az	−48	8a
6-CH_3O-1	−53 ± 2 (2)	6-CH_3O-Az	−47	*m*, *n*
6-CH_3-1	−15 (1)	6-CH_3-Az	−15	*m*, *n*
6-Br-1	6 ± 1 (2)	6-Br-Az	2	*m*
6-NC-1	62 ± 1 (3)	6-NC-Az	51	*m*

[a] λ_{max} (X-1) − λ_{max} (1); λ_{max} 1-OH (596 nm), 1-OAc (593 nm), 1-OTs (590 nm) in CH_2Cl_2. Polar solvent (CH_2Cl_2 and 95% EtOH) used except where noted. [b] λ_{max} (X-Az) − λ_{max} (Az-H); λ_{max} Az-H (580 nm in cyclohexane, 578 nm in CH_2Cl_2 or EtOH). Nonpolar solvent (cyclohexane and *n*-hexane) used except where noted. [c] Number of O-derivatives of 1-OH used; contains tosylates λ_{max} except where noted. [d] ROAc. [e] Solvent cyclohexane. [f] Solvent CCl_4. [g] Solvent CH_2Cl_2. [h] Solvent $CHCl_3$. [i] This work. [j] J. M. Richmond, Ph.D. Thesis, Kansas State University, 1974. [k] D. B. Gale, Ph.D. Thesis, University of Washington, 1957. [l] K. Hafner and C. Bernhard, *Justus Liebigs Ann. Chem.*, **625**, 108 (1959). [m] H. E. Petty, Ph.D. Thesis, Kansas State University, 1971. [n] K. Hafner and K-D. Asmus, *Justus Liebigs Ann. Chem.*, **671**, 31 (1964).

other series of these ring-substituted derivatives.

Overall, the additivity of the substituent effects holds very well. This is especially true with the 2-substituted derivatives of 1-OH, 1-OAc, and 1-OTs.

In the 3- and 6-substituted derivatives of 1, larger hypsochromic shifts are observed for the electron-withdrawing ring substituents compared to those measured for the corresponding monosubstituted azulenes (X-Az). This we attribute primarily to a solvent effect on λ_{max} where the effect is attenuated in the nonpolar solvent. This is amply demonstrated with 3-NC-1-OTs, λ_{max} 552 nm (95% EtOH), compared to 3-NC-1-OAc, λ_{max} 575 nm (cyclohexane).

The case of the 3-thiomethyl derivatives, 3-CH_3S-1, appears to be the most glaring inconsistency in the additivity of substituent effects on λ_{max} in Table I. We doubt that this magnitude of change ($\Delta\Delta\lambda_{max}$ = 21 nm) is due to a solvent effect since none is observed with 3-CH_3O-1 (CH_2Cl_2) vs. 1-CH_3O-Az (cyclohexane). It must be noted that absorption fine structure seen in cyclohexane is lost in CH_2Cl_2 solvent.

The reported visible spectrum of 1-thiomethylazulene (1-CH_3S-Az) in cyclohexane has three maxima of essentially identical intensities, 581 nm (ε 269), 599 (268), 627 (265), and 695 (141).[7] The above evidence and the fact that 1,3-bis(thiomethyl)azulene has $\Delta\lambda_{max}$ 47 nm (cyclohexane) leads us to conclude that the 599-nm maximum in 1-CH_3S-Az is the band to be associated with the 1-thiomethyl group when using the empirical Plattner's rules for predicting the visible spectra of substituted azulenes; for 1-CH_3S–, $\Delta\lambda_{max}$ is 19 nm.[29]

Experimental Section[27]

2-(1-Azulyl)ethanol (1-OH). A. Stepwise Construction of Side Chain.[4] The method of Anderson et al.[4] was used with certain modifications; relevant spectral data are included. 1-Azulylmethyltrimethylammonium iodide was obtained in 84% yield as purple needles: mp >230 °C; NMR (CD_3CN, internal Me_4Si) τ 1.0–2.8 (m, Az-H's, 7), 5.00 (s, CH_2, 2), and 6.90 (s, CH_3's, 9); uv–visible (95% EtOH) 649 nm (log ε 2.12), 591 (2.55), 554 (2.62), 351 (3.58), 336 (3.74), 328 (3.63), 287 (4.27), 282 (4.71), and 277 (4.76).

From 450 mg of the above quaternary iodide and 260 mg of KCN in 20 ml of absolute ethanol, we obtained 216 mg (95%) of 1-azulylacetonitrile: mp 54–55 °C (lit.[4] 43–44 °C); NMR (CCl_4, internal Me_4Si) τ 1.6–3.2 (m, Az-H's, 7) and 6.10 (s, CH_2, 2); uv–visible (CH_2Cl_2) 616 nm (log ε 2.51), 581 (2.55), 355 (3.44), 341 (3.66), 286 (4.62), 282 (4.67), and 277 (4.70).

Forty milliliters of a 0.6 M solution of potassium hydroxide in 50% aqueous ethanol was swept with N_2 for 2 h. To this solution heated under reflux was added 100 mg (0.6 mmol) of 1-azulylacetonitrile in 2 ml of THF and the mixture was heated under reflux for 7 h with a continuous, slow N_2 sweep. The solution was allowed to cool and 50 ml of water and 100 ml of ether were added. The layers were separated to remove a small trace of ether-soluble material. The aqueous layer was acidified with 5% hydrochloric acid and extracted with two 100-ml portions of ether. The combined ether layers were washed twice with equal volumes of water and dried ($MgSO_4$). The solvent was evaporated to afford 95 mg (86%) of 1-azulylacetic acid as a blue oil which crystallized as blue needles: mp 89.9–91.0 °C (lit.[4] 92–93 °C); ir (CCl_4) 3.0–3.3 (OH) and 5.85 μ (C=O); NMR (CCl_4, internal Me_4Si) τ −1.90 (s, OH, 1), 1.6–3.3 (m, Az-H's, 7), and 6.07 (s, CH_2, 2); uv–visible (CH_2Cl_2) 691 nm (log ε 2.05), 630 (2.47), 586 (2.53), 356 (3.43), 341 (3.67), 332 (3.53), 288 (4.64), 283 (4.70), and 277 (4.72).

Reduction of 150 mg of 1-azulylacetic acid with diborane gave 125 mg (90%) of 1-OH: mp 57–58 °C (lit.[4] 59–60 °C); ir (neat film) 2.95 (OH) and 9.63 μ (C–O); NMR (CCl_4, internal Me_4Si) τ 1.4–3.4 (m, Az-H's, 7), 6.26 (t, α-CH_2, 2), 6.86 (t, β-CH_2, 2), and 7.36 (s, OH, 1); uv–visible (CH_2Cl_2) 704 nm (log ε 1.93), 646 (2.39), 596 (2.46), 359 (3.32), 343 (3.63), 288 (4.58), 283 (4.67), and 278 (4.70); mass spectrum (70 eV, heated inlet) *m/e* (rel intensity) 172 (19, $M\cdot^+$), 141 (100), and 115 (16).

B. Direct β-Hydroxyethylation of Azulene.[5] The procedure utilizes ethylene oxide, azulene, and $AlCl_3$ in CH_2Cl_2. The major product is 1-OH along with a small amount of 1,3-bis(2-hydroxyethyl)azulene which are readily separated by chromatography on alumina.[5]

2-(1-Azulyl)ethyl Acetate (1-OAc). To 90 mg (0.52 mmol) of 1-OH dissolved in 3.0 ml of dry pyridine and cooled to 0 °C was added 0.6 ml of reagent grade acetic anhydride and the mixture was allowed to stir at 0 °C for 2 h. A mixture of 25 ml of ice-cold water and 10 ml of 5% hydrochloric acid was added and all of the blue color was extracted with three 20-ml portions of CH_2Cl_2. The combined organic layers were washed three times with ice-cold 5% hydrochloric acid and once with 100 ml of cold water, and dried ($MgSO_4$). The solvent volume was reduced and the residue was chromatographed on alumina[28] where CH_2Cl_2 eluted 103 mg (92%) of the acetate as a blue oil: ir (neat film) 5.70 (C=O) and 9.55 μ (C–O); NMR (CCl_4, internal Me_4Si) τ 1.6–3.3 (m, Az-H's, 7), 5.76 (t, α-CH_2, 2), 6.76 (t, β-CH_2, 2), 8.13 (s, CH_3, 3); uv–visible (CH_2Cl_2) 643 nm (log ε 2.41), 593 (2.49), 357 (3.38), 343 (3.67), 288 (4.60), 283 (4.70), and 278 (4.73); mass spectrum (70 eV, heated inlet) *m/e* (rel intensity) 214 (20, $M\cdot^+$), 154 (78), and 141 (100).

To 140 mg (0.66 mmol) of the acetate was added 150 mg (0.70 mmol) of TNB in 5.0 ml of ethyl acetate. The solvent volume was reduced in half and this mixture was added to a solution of 1.0 ml of ethyl acetate in 7.0 ml of hexane. The solution was cooled and the complex crystallized as large violet plates (172 mg, 62%). Repeated recrystallization afforded an analytical sample, mp 94.7–94.9 °C.

Anal. Calcd for $C_{20}H_{17}N_3O_8$: C, 56.21; H, 4.01. Found: C, 56.19; H, 3.84.

2-(1-Azulyl)ethyl Tosylate (1-OTs). To a solution of 115 mg (0.67 mmol) of 1-OH dissolved in 3.5 ml of dry ether and cooled to 0 °C was added 40 mg (0.61 mmol) of powdered KOH followed by 130 mg (0.70 mmol) of *p*-toluenesulfonyl chloride. The mixture was allowed to stir at 0 °C for 5 h and then 20 ml of ice-cold water and 20 ml of ether were added. The layers were separated, the ether solution was dried (K_2CO_3), and the solvent volume was reduced. The residue was immediately chromatographed on deactivated (7% H_2O) alumina[28] where CH_2Cl_2 eluted a blue band which afforded 155 mg of crude tosylate as an unstable blue oil upon solvent volume reduction.

The crude tosylate was dissolved in 5.0 ml of ethyl acetate containing 150 mg (0.70 mmol) of TNB. The solvent volume was reduced in half, 3.0 ml of hexane was added, and the solution was

cooled to freezer temperature. Large brown crystals (175 mg, 67%) were formed upon standing: mp 76.4–76.7 °C; ir (neat film) 6.15 (aryl C–C), 7.47 (S–O_{asym}), and 8.50 μ (S–O_{sym}); NMR ($CDCl_3$, internal Me_4Si) τ 0.60 (s, TNB-H's, 3), 1.4–3.2 (m, azulyl and tosyl H's, 11), 5.66 (t, α-CH_2, 2), 6.56 (t, β-CH_2, 2), and 7.56 (s, CH_3, 3); uv-visible (CH_2Cl_2) 701 nm (log ϵ 2.03), 637 (2.45), 590 (2.52), 357 (3.42), 342 (3.70), 333 (3.56), 288 (4.63), 283 (4.70), and 278 (4.73); mass spectrum (20 eV, heated inlet) *m/e* (rel intensity) 326 (20, $M^{\cdot+}$), 154 (58), and 141 (100).

Anal. Calcd for $C_{25}H_{21}N_3O_9S$: C, 55.65; H, 3.92. Found: C, 55.41; H, 4.02.

1-Azulyl Benzoate.[11] To a solution of 1.00 g (7.83 mmol) of azulene in 50 ml of CCl_4 was added 945 mg (3.91 mmol) of recrystallized benzoyl peroxide. The mixture was heated under reflux with a dry, oxygen-free, nitrogen atmosphere for 2.5 h. The solvent volume was reduced, and the residue chromatographed on Florisil (Fisher, 60–100 mesh). Elution with hexane afforded a violet band of unreacted azulene, 500 mg. CCl_4 eluted a narrow, blue band and a faint, green band, neither of which was further investigated, and finally a broad, blue band. CH_2Cl_2 eluted a green band.

The broad, blue band gave 291 mg (15%, 30% net) of the title compound, mp 61.0–62.0 °C (lit.[11] mp 62.5–63.5 °C). (See paragraph at end of paper regarding supplementary material.)

The green band afforded 300 mg (10%, 20% net) of 1,3-azulene dibenzoate. Crystallization from ether yielded green crystals: mp 129.5–130.5 °C (lit.[11] mp 132–134 °C); ir (KBr) 5.75 μ (s, C=O); NMR ($CDCl_3$, internal Me_4Si) τ 1.56–2.13 (m, 6) and 2.20–3.33 (m, 10).

Anal. Calcd for $C_{24}H_{16}O_4$: C, 78.25; H, 4.38. Found: C, 78.23; H, 4.72.

1-Methoxyazulene. The preparation of 230 mg of this compound was accomplished in 70% yield by the method of Replogle[11] from 516 mg (2.08 mmol) of 1-azulyl benzoate, 10 ml of methyl iodide, and 10 ml of 1.9 M methanolic sodium hydroxide in 100 ml of dry (BaO) DMF under a nitrogen atmosphere for 6 h at room temperature. The emerald-green oil crystallized from hexane as green needles, mp 29.5–30.0 °C (lit.[11] mp 26–28 °C). (See paragraph at end of paper regarding supplementary material.)

For analysis a TNB complex was prepared and crystallized from 1:1 CH_2Cl_2–hexane to afford long, fine, black needles, mp 134.0–135.0 °C.

Anal. Calcd for $C_{17}H_{13}O_7N_3$: C, 54.99; H, 3.53. Found: C, 54.94; H, 3.63.

2-(3-Methoxy-1-azulyl)ethanol (3-CH_3O-1-OH). A mixture of 153 mg (1.5 mmol) of *N,N,N',N'*-tetramethyldiaminomethane, 30 mg (1.0 mmol) of paraformaldehyde, and 4 ml of acetic acid was heated to develop a clear solution. This solution, cooled to room temperature, was added dropwise with stirring to 225 mg (1.42 mmol) of 1-methoxyazulene in 20 ml of CH_2Cl_2 at 0 °C. This mixture was allowed to stir for 1 h at 0 °C, placed in the refrigerator overnight, and then diluted with 100 ml of CH_2Cl_2, washed with three 100-ml portions of water, and dried (Na_2SO_4), the solvent volume was reduced, and the green residue was chromatographed on alumina.[28] CH_2Cl_2 eluted a yellow band that was not investigated, and developed a broad, blue band which was eluted with anhydrous ether. The solvent volume of the blue eluate was reduced, and the residue, dissolved in 10 ml of absolute ethanol, treated with an excess of methyl iodide. Crystallization afforded 269 mg (53%) of the quaternary iodide, as green crystals: mp >300 °C; ir (KBr) no characteristic absorptions; λ_{max} (95% ethanol) 286 nm (log ϵ 4.61), 360 (3.62), 377 (3.62), and 697 (2.88).

Anal. Calcd for $C_{15}H_{20}ONI$: C, 50.43; H, 5.64. Found: C, 50.20; H, 5.70.

To 269 mg (0.755 mmol) of quaternary ammonium iodide (above) in 25 ml of absolute ethanol was added 145 mg (2.40 mmol) of KCN. The mixture was heated under reflux for 50 min, diluted with 100 ml of water, and extracted with 50 ml of ether. The ethereal layer was washed with two 50-ml portions of water and dried (Na_2SO_4), the solvent volume was reduced, and the green residue was chromatographed on basic alumina.[28] CH_2Cl_2 eluted a broad, blue band followed by a brown band. Continued elution with $CHCl_3$ developed a narrow, blue band. Only the first, blue band was examined, which afforded 115 mg (78%) of 3-methoxy-1-azulylacetonitrile. Crystallization from CCl_4 gave green needles, mp 81.8–82.0 °C. (See paragraph at end of paper regarding supplementary material.)

Anal. Calcd for $C_{13}H_{11}ON$: C, 79.16; H, 5.62; N, 7.10. Found: C, 78.89; H, 5.49; N, 6.82.

Following the above procedure (a) in the preparation of 1-OH, 175 mg of the above nitrile in 20 ml of THF was hydrolyzed with base for 18 h under reflux and an N_2 atmosphere. Work-up gave 160 mg (83%) of 3-methoxy-1-azulylacetic acid, mp 115–118 °C. (See paragraph at end of paper regarding supplementary material.)

Sodium borohydride (220 mg, 5.8 mmol) was added to a solution of 160 mg (0.74 mmol) of 3-methoxy-1-azulylacetic acid in 20 ml of dry tetrahydrofuran. When the evolution of hydrogen had ceased, a solution of 3 ml of boron trifluoride etherate in 20 ml of dry tetrahydrofuran was added dropwise over a period of 10–15 min to the stirred mixture. The green mixture was stirred for 1.5 h as the color gradually changed to blue. The mixture was then acidified by the dropwise addition of 20 ml of 10% hydrochloric acid, diluted with 100 ml of water, and extracted with two 100-ml portions of ether. The combined ethereal layers were washed with a 100-ml portion of water. The extracts were dried (Na_2SO_4), the solvent volume reduced, and the residue chromatographed on alumina[28] where $CHCl_3$ eluted a single, blue band, which afforded 145 mg (97%) of 3-CH_3O-1-OH, an emerald-green oil. (See paragraph at end of paper regarding supplementary material.)

For analysis a TNB complex was prepared and crystallized from 1:1 ethyl acetate–hexane to yield brown needles: mp 147.0–148.0 °C; ir (KBr) 3.05 (m, O–H) and 9.60 μ (m, C–O); λ_{max} (CH_2Cl_2) 291 nm (log ϵ 4.62), 362 (3.68), 378 (3.64), 695 (2.52), and 770 (2.44) (sh).

Anal. Calcd for $C_{19}H_{17}O_8N_3$: C, 54.94; H, 4.13. Found: C, 54.99; H, 4.26.

2-(3-Methoxy-1-azulyl)ethyl Tosylate (3-CH_3O-1-OTs). 3-CH_3O-1-OH (145 mg, 0.72 mmol) was converted to its tosylate ester by the method described for 1-OTs. After work-up, the residue was chromatographed on deactivated (4.6% water) basic alumina[28] with CH_2Cl_2. A blue band was eluted affording 230 mg (90%) of 3-CH_3O-1-OTs as a green oil.

This rather unstable tosylate was converted to its TNB complex which was obtained as long, black needles, mp 98.5–99.5 °C. (See paragraph at end of paper regarding supplementary material.)

Anal. Calcd for $C_{26}H_{23}O_{10}N_3S$: C, 54.83; H, 4.07; N, 7.38. Found: C, 54.55; H, 4.12; N, 7.52.

2-(3-Methyl-1-azulyl)ethanol (3-CH_3-1-OH). To a solution of 200 mg (1.16 mmol) of 1-OH in 10 ml of CH_2Cl_2 and 10 ml of acetic acid, cooled to 0 °C, was added 135 mg (1.32 mmol) of *N,N,N',N'*-tetramethylmethylenediamine dissolved in 4 ml of acetic acid. This mixture was stirred at 0 °C for 2 h, diluted with 50 ml of ice-cold water and 50 ml of 5% hydrochloric acid, and extracted with 50 ml of ether. The aqueous layer was neutralized with dilute potassium hydroxide and extracted with two 100-ml portions of ether. The combined extracts were dried (K_2CO_3), the solvent volume reduced, and the residue dissolved in 4 ml of absolute ethanol and cooled to 0 °C. To this solution was added 3 ml of methyl iodide. Crystallization afforded 375 mg (87%) of the ammonium salt.

To a solution of 375 mg (1.01 mmol) of the ammonium salt in 20 ml of absolute ethanol was added 60 mg (1.59 mmol) of $NaBH_4$ and the mixture was allowed to stir at room temperature for 10 h. A 1-ml aliquot of the mixture added to 1 ml of ether and 2 ml of water yielded a violet color in the aqueous layer, indicating incomplete conversion. The reaction mixture was then heated at reflux for 7 min, diluted with 100 ml of water, and extracted with three 100-ml portions of ether. The combined extracts were dried (K_2CO_3), the solvent volume reduced, and the residue chromatographed on deactivated (6% water) basic alumina[28] with acid-free (alumina) benzene. A broad, blue band eluted that was followed closely by a second blue band that was not investigated. The first blue band afforded 95 mg (51%) of 3-CH_3-1-OH as a blue oil that was unstable in the presence of trace amounts of acid. (See paragraph at end of paper regarding supplementary material.)

For analysis a TNB complex was prepared and crystallized from 1:1 ethyl acetate–hexane. Two recrystallizations afforded fine, long brown needles: mp 135.5–136.5 °C; ir (KBr) 3.08 (m, O–H) and 9.58 μ (m, C–O); λ_{max} (95% ethanol) 281 nm (log ϵ 4.76), 334 (3.55) (sh), 349 (3.76), 365 (3.63), 625 (2.50), 660 (2.43) (sh), 685 (2.40), and 765 (1.95).

Anal. Calcd for $C_{19}H_{17}O_7N_3$: C, 57.14; H, 4.29; N, 10.52. Found: C, 57.36; H, 4.15; N, 10.45.

2-(3-Methyl-1-azulyl)ethyl Tosylate (3-CH_3-1-OTs). The tosylate ester was prepared from 95 mg of 3-CH_3-1-OH by the method for 1-OTs. Chromatography on deactivated (4.6% H_2O) alumina[28] with acid-free (Al_2O_3) CH_2Cl_2 eluted a single band affording 167 mg (96%) of 3-CH_3-1-OTs.

This unstable tosylate was dissolved in 1.5 ml of ethyl acetate containing 107 mg (0.50 mmol) of TNB. An equal volume of hexanes was added and the solution cooled to afford brown-violet nee-

dles of the title compound, mp 81.0–81.5 °C. (See paragraph at end of paper regarding supplementary material.)

Anal. Calcd for $C_{26}H_{23}O_9N_3S$: C, 56.41; H, 4.19. Found: C, 56.70; H, 4.05.

2-(3-Thiocyano-1-azulyl)ethyl Acetate (3-SCN-1-OAc). A solution of 35 mg (0.16 mmol) of 1-OAc in 5 ml of CCl_4 was cooled to 0 °C. To this mixture was added a solution of thiocyanogen[6] (100 mg of lead thiocyanate in 5.0 ml of CCl_4 and Br_2 added to yield a residual red color which was removed with 10 mg more of lead thiocyanate and filtered) and the resulting mixture was allowed to stir at 0 °C for 3 h. This solution was then poured onto a column of basic alumina[28] where CH_2Cl_2 eluted 38 mg (89%) of the title compound as a blue-violet solid which afforded long violet needles upon recrystallization from CH_2Cl_2–hexane, mp 94.2–94.4 °C. (See paragraph at end of paper regarding supplementary material.)

Anal. Calcd for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83. Found: C, 66.55; H, 4.96.

2-(3-Methylthio-1-azulyl)ethyl Acetate (3-CH_3S-1-OAc). A solution of 24 mg (0.09 mmol) of 3-SCN-1-OAc dissolved in 5.0 ml of methanol was cooled to 0 °C. The solution was continually swept with O_2-free nitrogen gas. To this solution was added 1.0 ml of methyl iodide (excess) and 100 mg (1.78 mmol) of potassium hydroxide in 5.0 ml of 50% aqueous methanol, and the solution was allowed to stir at 0 °C for 2 h. A mixture of 30 ml of ice-cold water and 50 ml of ether was added and the layers were separated. The aqueous layer was again extracted with 50 ml of ether to remove the last trace of blue color. The combined ether layers were washed with three 50-ml portions of cold water and dried ($MgSO_4$). The solvent volume was reduced and the residue was chromatographed on alumina[28] where $CHCl_3$ eluted 16 mg (84%) of 3-CH_3S-1-OH as an unstable, green oil. (See paragraph at end of paper regarding supplementary material.)

The crude 3-CH_3S-1-OH (77 mg, 0.35 mmol) was then acetylated with acetic anhydride in pyridine at 0 °C. After normal workup, the acetate was chromatographed on alumina[28] where CH_2Cl_2 eluted 81 mg (88%) of 3-CH_3S-1-OAc as a green oil which crystallized on standing, mp 39.2–40.0 °C. (See paragraph at end of paper regarding supplementary material.)

To 60 mg (0.23 mmol) of 3-CH_3S-1-OAc dissolved in 3.0 ml of ethyl acetate to which had been added 90 mg (0.42 mmol) of TNB, an equal volume of hexanes was added and this solution was placed in a refrigerator where crystallization afforded 65 mg (61%) of long, brown-black needles, mp 85.6–85.8 °C.

Anal. Calcd for $C_{21}H_{19}N_3O_8S$: C, 53.27; H, 4.04. Found: C, 53.21; H, 4.01.

2-(3-Methylthio-1-azulyl)ethyl Tosylate (3-CH_3S-1-OTs). 3CH_3S-1-OH (70 mg, 0.32 mmol) was converted to its tosylate ester by the method given for 1-OTs. Chromatography on deactivated (6% H_2O) alumina[28] developed a blue band of the tosylate which eluted with CH_2Cl_2. Evaporation of the solvent gave the tosylate as a green, unstable oil.

The tosylate ester was converted to its TNB complex which crystallized as long, black needles, 175 mg (94%). Recrystallization was repeated several times to afford an analytical sample, mp 98.2–98.4 °C. (See paragraph at end of paper regarding supplementary material.)

Anal. Calcd for $C_{26}H_{23}N_3O_9S_2$: C, 53.33; H, 3.96. Found: C, 53.31; H, 3.97.

2-(3-Bromo-1-azulyl)ethyl Acetate (3-Br-1-OAc). To a solution of 25 mg (0.11 mmol) of 1-OAc in 3.0 ml of dry benzene was added 25 mg (0.14 mmol) of *N*-bromosuccinimide and the mixture was allowed to stir for 2 min at room temperature. This solution was poured onto a column of alumina[28] where CH_2Cl_2 eluted a blue band which afforded 33 mg (96%) of 2-(3-bromo-1-azulyl)ethyl acetate as a green oil: ir (neat film) 5.72 μ (C=O); NMR (CCl_4, internal Me_4Si) τ 1.6–3.2 (m, Az-H's, 6), 5.73 (t, α-CH_2, 2), 6.67 (t, β-CH_2, 2), 7.97 (s, CH_3, 3).

3-Br-1-OAc (66 mg, 0.23 mmol) was converted to its TNB complex which crystallized as long, brown needles (75 mg, 83%). Repeated recrystallizations from ethyl acetate–hexane afforded an analytical sample: mp 84.7–85.1 °C; uv–visible (CH_2Cl_2) 609 nm (log ϵ 2.58), 364 (3.80), 348 (3.84), 340 (3.74), 295 (4.73), and 285 (4.78).

Anal. Calcd for $C_{20}H_{16}N_3BrO_8$: C, 47.45; H, 3.19. Found: C, 47.46; H, 3.11.

2-(3-Bromo-1-azulyl)ethyl Tosylate (3-Br-1-OTs). To 100 mg (0.20 mmol) of 3-Br-1-OAc-TNB complex dissolved in a mixture of 4.0 ml of ethanol, 2.0 ml of THF, and 0.5 ml of water was added 0.30 g (5.4 mmol) of KOH and the solution was cooled to 0 °C. The mixture was allowed to stir at 0 °C for 1 h and then 100 ml of ice-cold water and 50 ml of ether were added. The layers were separated and ether extraction of the aqueous layer was repeated. The combined ether layers were washed with two 50-ml portions of ice-cold water and dried ($MgSO_4$), and the solvent volume was reduced. The residue was chromatographed on alumina[28] where $CHCl_3$ eluted 35 mg (88%) of 3-Br-1-OH as an unstable, green oil. (See paragraph at end of paper regarding supplementary material.)

3-Br-1-OH (35 mg, 0.14 mmol) was converted to its tosylate ester by the method given for 1-OTs. It was chromatographed on deactivated (6% H_2O) alumina[28] where CH_2Cl_2 eluted it as a blue band affording 61 mg of crude 3-Br-1-OTs. The tosylate was added to 2.0 ml of ethyl acetate containing 60 mg (0.28 mmol) of TNB. An equal volume of hexanes was added and the mixture was cooled. Brown-pink crystals formed after 3 h to afford 61 mg (72%) of the complex. This sample was recrystallized several times from ethyl acetate–hexane, mp 86.5–86.6 °C. (See paragraph at end of paper regarding supplementary material.)

Anal. Calcd for $C_{25}H_{20}BrN_3O_9$: C, 48.55; H, 3.26. Found: C, 48.74; H, 3.28.

2-(3-Acetyl-1-azulyl)ethyl Acetate (3-CH_3CO-1-OAc). To a solution of 35 mg (0.16 mmol) of 1-OAc in 3.0 ml of dry nitrobenzene was added 0.6 ml of reagent grade acetic anhydride followed by 3 drops of stannic chloride. The solution was allowed to stir for 7 min at room temperature and then a mixture of 20 ml of ice-cold water and 20 ml of CCl_4 was added. The layers were separated and the CCl_4 extraction on the aqueous layer was repeated. The combined organic layers were washed with three 20-ml portions of water and dried ($MgSO_4$). The solution was filtered directly onto a column of alumina[28] where elution with $CHCl_3$ afforded 36 mg (86%) of the acetate as a lavendar oil: ir (neat film) 5.71 (ester C=O) and 6.03 μ (ketone C=O).

To 42 mg (0.16 mmol) of 3-CH_3CO-1-OAc dissolved in 2.0 ml of ethyl acetate was added 60 mg (0.28 mmol) of TNB. An equal volume of hexanes was added and the solution was cooled to induce crystallization. The complex (61 mg, 79%) crystallized as long, red-brown needles and was crystallized several more times, mp 93.2–93.5 °C. (See paragraph at end of paper regarding supplementary material.)

Anal. Calcd for $C_{22}H_{19}N_3O_9$: C, 56.21; H, 4.08. Found: C, 56.10; H, 4.11.

2-(3-Acetyl-1-azulyl)ethyl Tosylate (3-CH_3CO-1-OTs). 3-CH_3CO-1-OAc (50 mg, 0.19 mmol) was hydrolyzed to 3-CH_3CO-1-OH in quantitative yield as per 3-Br-1-OAc → 3-Br-1-OH conditions. $CHCl_3$ eluted 3-CH_3CO-1-OH from alumina[28] chromatography as an unstable, green semisolid. (See paragraph at end of paper regarding supplementary material.)

3-CH_3CO-1-OH (88 mg, 0.41 mmol) was converted to its tosylate ester by the method given for 1-OTs. It was chromatographed on alumina[28] where CH_2Cl_2 eluted it as a purple band giving 90 mg (53%) of 3-CH_3CO-1-OTs as long, green needles, mp 91.7–92.0 °C. (See paragraph at end of paper regarding supplementary material.)

Anal. Calcd for $C_{21}H_{20}O_4S$: C, 68.45; H, 5.47. Found: C, 68.47; H, 5.61.

2-(3-Cyano-1-azulyl)ethyl Acetate (3-CN-1-OAc). Method A. A mixture of 250 mg (0.85 mmol) of 3-Br-1-OAc and 114 mg (1.28 mmol) of CuCN in 10 ml of dry DMF was heated at 135 °C for 10 h under an N_2 atmosphere. The mixture was cooled, diluted with 100 ml of benzene, and washed with six 100-ml portions of warm, aqueous NaCN (prepared from 600 ml of warm water and 20 g of NaCN). The organic layer was washed with 100 ml of water and dried (Na_2SO_4), the solvent volume reduced, and the residue chromatographed on alumina.[28] Elution with 1:1 CCl_4–CH_2Cl_2 developed a blue band that afforded 150 mg (60% recovery) of unreacted 3-Br-1-OAc. Continued elution with CH_2Cl_2 yielded a violet band that afforded 65 mg (32%, 80% net) of 3-CN-1-OAc. Crystallization from CCl_4 afforded violet crystals, mp 57.0–57.5 °C. (See paragraph at end of paper regarding supplementary material.)

Anal. Calcd for $C_{15}H_{13}O_2N$: C, 75.29; H, 5.48. Found: C, 75.08; H, 5.49.

Method B. Stannic chloride (3.48 g, 13.3 mmol) was added to 1.410 g (13.3 mmol) of BrCN with cooling and stirring under an N_2 atmosphere. A white suspension appeared, and the mixture was stirred at room temperature for 10 min. To this mixture was added dropwise 285 mg (1.33 mmol) of 1-OAc in 20 ml of dry ether, and the mixture allowed to stir at room temperature for 18 h. The mixture was diluted with 50 ml of 5% hydrochloric acid and extracted

with three 50-ml portions of $CHCl_3$. The combined, blue extracts were washed with 50 ml of 5% aqueous sodium bicarbonate which was accompanied by a color change to forest green. The extracts were washed with 50 ml of water and dried (Na_2SO_4), the solvent volume reduced, and the residue chromatographed on basic alumina[28] with 1:1 CCl_4–CH_2Cl_2. A blue band eluted that was followed by a yellow-green band. Further elution with CH_2Cl_2 yielded a violet band and $CHCl_3$ afforded a dark-green band. Only the violet band, that afforded 60 mg (19%) of the title compound, was investigated. The NMR and ir spectra were identical with those obtained from method A.

2-(3-Cyano-1-azulyl)ethyl Tosylate (3-CN-1-OTs). 3-CN-1-OAc (125 mg, 0.57 mmol) was hydrolyzed to 3-CN-1-OH as per the 3-Br-1-OAc → 3-Br-1-OH conditions. The alcohol was chromatographed on alumina[28] where $CHCl_3$ eluted it as a violet band which afforded 110 mg (99%) of 3-CN-1-OH as a violet oil. (See paragraph at end of paper regarding supplementary material.)

A TNB complex was prepared in the usual way and recrystallized from 1:1 ethyl acetate–hexane giving red-brown plates, mp 84.0–84.5 °C. Examination of the NMR spectrum of this derivative revealed it to be a 2:1 complex, 3-CN-1-OH–2TNB; TNB complexes of azulenes in other than 1:1 ratios are known.[29] The log ϵ values below are calculated assuming a 2:1 complex ratio: λ_{max} (CH_2Cl_2) 285 nm (log ϵ 4.54), 290 (4.65), 295 (4.60), 302 (4.74), 344 (3.71), 354 (3.80), 371 (3.92), 563 (2.63), 604 (2.57) (sh), and 665 (2.11) (sh).

3-CN-1-OH (110 mg, 0.56 mmol) was converted to its tosylate ester by the method given for 1-OTs. It was chromatographed on deactivated (6% H_2O)[28] alumina where CH_2Cl_2 eluted it as a violet band giving 175 mg (89%) of 3-CN-1-OTs as violet needles, mp 111.0–111.5 °C. (See paragraph at end of paper regarding supplementary material.)

Anal. Calcd for $C_{20}H_{17}O_3NS$: C, 68.35; H, 4.88. Found: C, 68.49; H, 4.93.

2-(3-Nitro-1-azulyl)ethyl Acetate (3-NO_2-1-OAc). To a solution of 44 mg (0.20 mmol) of 1-OAc in 2 ml of pyridine was added 0.5 ml of 0.6 M tetranitromethane in absolute ethanol and the mixture was allowed to stir at room temperature for 15 min. A mixture of 20 ml of ice-cold water and 25 ml of $CHCl_3$ was added to the red-brown solution. The layers were separated and the aqueous layer was extracted twice more with $CHCl_3$. The combined organic layers were washed with three 30-ml portions of 5% hydrochloric acid and 100 ml of water, and dried ($MgSO_4$). The solvent volume was reduced and the residue was chromatographed on alumina[28] where CH_2Cl_2 eluted 47 mg (89%) of 3-NO_2-1-OAc which was recrystallized several times from ethyl acetate, mp 98.6–99.0 °C. (See paragraph at end of paper regarding supplementary material.)

Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05. Found: C, 64.61; H, 4.82.

2-(3-Nitro-1-azulyl)ethanol (3-NO_2-1-OH). 1-OH (97 mg, 0.43 mmol) was nitrated with tetranitromethane as above in the preparation of 3-NO_2-1-OAc. It was chromatographed on alumina[28] where chloroform eluted 0.112 g (92%) of 3-NO_2-1-OH as a red oil which crystallized on standing, mp 105.0–106.0 °C. (See paragraph at end of paper regarding supplementary material.)

An α-naphthyl urethane was prepared in pyridine. It was chromatographed on alumina[28] where CH_2Cl_2 eluted it as an orange band. Repeated recrystallizations from 1:1 CCl_4–CH_2Cl_2 gave orange-red crystals, mp 184.2–184.5 °C.

Anal. Calcd for $C_{23}H_{18}N_2O_4$: C, 71.48; H, 4.69. Found: C, 71.21; H, 4.66.

2-(3-Nitro-1-azulyl)ethyl Tosylate (3-NO_2-1-OTs). A solution of 108 mg (0.50 mmol) of 3-NO_2-1-OH in 2.0 ml of dry pyridine was cooled to 0 °C. To this solution was added 150 mg (0.79 mmol) of toluenesulfonyl chloride and the mixture was allowed to stir at 0 °C for 3 h. A mixture of 20 ml of ice-cold water and 20 ml of $CHCl_3$ was added and the layers were separated. The aqueous layer was extracted with two 20-ml portions of $CHCl_3$ to remove the remaining orange color. The combined organic layers were washed with three 50-ml portions of ice-cold, 5% hydrochloric acid and once with 50 ml of cold water, and dried ($MgSO_4$). The solvent volume was reduced and the residue chromatographed on alumina[28] where CH_2Cl_2 eluted 170 mg (92%) of 3-NO_2-1-OTs which was subsequently recrystallized from hexane–CH_2Cl_2 to afford red plates, mp 124.4–124.9 °C. (See paragraph at end of paper regarding supplementary material.)

Anal. Calcd for $C_{19}H_{17}NO_5S$: C, 61.43; H, 4.61. Found: C, 61.14; H, 4.56.

Dimethyl 2-Methoxy-1,3-azulenedicarboxylate.[12a] To 150 ml of dry methanol [distilled from $Mg(OCH_3)_2$] was added 575 mg (25.0 mg-atoms) of sodium. When the sodium had dissolved, 1.58 g (5.15 mmol) of diethyl 2-chloro-1,3-azulenedicarboxylate[1a] in 100 ml of dry methanol was added. This mixture was heated under reflux with stirring for 2.5 h, the solvent volume reduced, and the residue chromatographed on alumina.[28] Benzene eluted a single, red band that afforded 1.330 g (94%) of the title compound. Recrystallization from methanol yielded needles, mp 64.5–65.5 °C (lit.[12a] mp 60–62 °C). (See paragraph at end of paper regarding supplementary material.)

Anal. Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.14. Found: C, 65.90; H, 5.14.

2-Methoxyazulene.[12a] To 500 mg (1.83 mmol) of dimethyl 2-methoxy-1,3-azulenedicarboxylate in 5 ml of ethanol was added 1.00 g (17.9 mmol) of potassium hydroxide in 10 ml of water. This mixture was heated under reflux with stirring for 2 h as the color changed from orange to red, transferred to a centrifuge tube, and acidified with 6 M hydrochloric acid. The resultant solid was collected, transferred with acetone into a large sublimation tube, and dried overnight at room temperature with an air stream.

This sample was heated to 200 °C (100 Torr) and a rose-violet sublimate formed on the condenser. The sublimate was removed with hexane and chromatographed on alumina.[28] Hexane developed a rose-colored band that was eluted with benzene to afford 230 mg (80%) of the title compound. Crystallization from methanol yielded red-violet crystals, mp 79.0–80.0 °C (lit.[12a] mp 82–83 °C). (See paragraph at end of paper regarding supplementary material.)

Anal. Calcd for $C_{11}H_{10}O$: C, 83.51; H, 6.37. Found: C, 83.60; H, 6.06.

2-(2-Methoxy-1-azulyl)ethyl Acetate (2-CH_3O-1-OAc). To 290 mg (1.83 mmol) of 2-methoxyazulene in 20 ml of CH_2Cl_2 with stirring at 0 °C was added 505 mg (3.80 mmol) of $AlCl_3$. An immediate change from a rose-red to a deep-red color occurred. After stirring for 5 min 8 ml of a 2% solution (v/v) of ethylene oxide was added and a red-brown coloration was observed. The mixture was stirred for an additional 20 min, diluted with 100 ml of ice-cold water, and extracted with three 50-ml portions of CH_2Cl_2. The combined extracts were washed with eight 75-ml portions of 10% hydrochloric acid and dried (Na_2SO_4), the solvent volume reduced, and the residue chromatographed on alumina[28] with CH_2Cl_2 which eluted a red band that afforded 178 mg of unreacted 2-methoxyazulene. $CHCl_3$ eluted a violet band that yielded 130 mg (35%, 92% net) of crude 2-CH_3O-1-OH.

2-CH_3-1-OH was acetylated with acetic anhydride in pyridine at 0 °C. After normal work-up, the acetate was chromatographed on alumina[28] with 4:1 C_6H_6–CH_2Cl_2. A violet band eluted and was rechromatographed giving the acetate in 60% overall yield which crystallized from hexane as fine, violet needles, mp 25.0–27.0 °C. (See paragraph at end of paper regarding supplementary material.)

For analysis a TNB complex was prepared and crystallized from 1:1 ethyl acetate–hexane to afford red-brown needles, mp 106.0–106.5 °C.

Anal. Calcd for $C_{21}H_{19}O_9N_3$: C, 55.14; H, 4.19. Found: C, 54.95; H, 4.30.

2-(2-Methoxy-1-azulyl)ethanol (2-CH_3O-1-OH). To 123 mg (0.50 mmol) of 2-CH_3O-1-OAc dissolved in 4 ml of ethanol and 0.5 ml of water was added 300 mg (5.4 mmol) of potassium hydroxide. This mixture was stirred at 0 °C for 2 h, diluted with 100 ml of ice-cold water, and extracted with three 50-ml portions of ether. The combined ether layers were washed once with 100 ml of water and dried (Na_2SO_4), and the solvent volume was reduced. The residue was chromatographed on alumina[28] where $CHCl_3$ eluted a single, violet-red band that afforded 95 mg (94%) of a violet oil. (See paragraph at end of paper regarding supplementary material.)

For analysis a TNB complex was prepared and crystallized from 1:1 ethyl acetate–hexane to afford red plates: mp 131.0–132.0 °C; λ_{max} (CH_2Cl_2) 283 nm (log ϵ 4.72), 293 (4.81), 318 (3.89), 345 (3.61), 361 (3.69), 375 (3.51), 535 (2.35), 570 (2.14), and 625 (1.69).

Anal. Calcd for $C_{19}H_{17}O_8N_3$: C, 54.94; H, 4.13. Found: C, 54.95; H, 4.15.

2-(2-Methoxy-1-azulyl)ethyl Tosylate (2-CH_3O-1-OTs). 2-CH_3O-1-OH (95 mg, 0.47 mmol) was converted to its tosylate ester by the method given for 1-OTs. It was chromatographed on deactivated (4.5% H_2O) alumina[28] where CH_2Cl_2 eluted it as a violet band yielding 140 mg (84%) of 2-CH_3O-1-OTs as a violet oil which crystallized on standing.

This unstable solid was converted to a TNB complex which crystallized as red-brown microcrystals, mp 96.5–97.5 °C. (See paragraph at end of paper regarding supplementary material.)

Anal. Calcd for $C_{26}H_{23}O_{10}N_3S$: C, 54.83; H, 4.07; N, 7.38. Found: C, 55.15; H, 3.99; N, 7.55.

2-Methylazulene. This was prepared by the method of Nozoe et al.[12a] using the thermal decarboxylation procedure as given above in the synthesis of 2-methoxyazulene, 260 °C (100 Torr). After chromatography, a 42% yield of 2-methylazulene was obtained, violet crystals, mp 48–49 °C (lit.[12a] mp 49–50 °C). (See paragraph at end of paper regarding supplementary material.)

For analysis a TNB complex was prepared and crystallized from 1:1 hexane–ethyl acetate, mp 42.5–43.5 °C.

Anal. Calcd for $C_{17}H_{13}O_6N_3$: C, 57.49; H, 3.69; N, 11.83. Found: C, 57.60; H, 4.03; N, 11.60.

2-(2-Methyl-1-azulyl)ethanol (2-CH_3-1-OH). Following the direct β-hydroxyethylation procedure described for the synthesis of 2-CH_3O-1-OAc, 124 mg (0.88 mmol) of 2-methylazulene and 70 mg of $AlCl_3$ in 30 ml of CH_2Cl_2 at 0 °C was treated with 5 ml of a 2% solution of ethylene oxide in CH_2Cl_2. After work-up the residue was chromatographed on alumina.[28] CH_2Cl_2 eluted a violet band to afford 100 mg of unreacted 2-methylazulene. $CHCl_3$ eluted a blue band, and a second smaller blue band was removed with absolute ethanol. Rechromatography of the first blue band afforded 25 mg (15%, 75% net) of 2-CH_3-1-OH as a blue band. (See paragraph at end of paper regarding supplementary material.)

A TNB complex was prepared for analysis and crystallized from 1:1 ethyl acetate–hexane to afford red-brown crystals: mp 144.0–144.5 °C; λ_{max} (CH_2Cl_2) 281 nm (log ε 4.68), 289 (4.76), 304 (3.74), 334 (3.50), 349 (3.61), 576 (2.36), 615 (2.30), and 687 (1.83).

Anal. Calcd for $C_{19}H_{17}O_7N_3$: C, 57.14; H, 4.29. Found: C, 57.20; H, 4.10.

The second, smaller, blue band afforded 10 mg (5%, 25% net) of 1,3-bis(2-hydroxyethyl)-2-methylazulene: NMR ($CDCl_3$, internal Me_4Si) τ 1.82 [d (J = 8.5 Hz), $C_{4,8}$ H's, 2], 2.57–2.84 (m, C_6 H, 1), 3.00 [t (J = 8.5 Hz), $C_{5,7}$ H's, 2], 6.25 (t (J = 6 Hz), α-CH_2, 4], 6.75 [t (J = 6 Hz), β-CH_2, 4], 7.47 (s, CH_3, 3), and 7.92 (s, OH, 2).

A TNB complex was prepared for analysis and crystallized from 1:1 ethyl acetate–hexane to afford red-brown crystals: mp 122–123 °C; ir (KBr) 3.00 (s, O–H) and 9.60 μ (s, C–O); λ_{max} (CH_2Cl_2) 287 nm (log ε 4.70), 294 (4.75), 307 (3.90), 338 (3.54), 353 (3.68), 369 (3.12), 595 (2.40), 635 (2.34), and 710 (1.90).

Anal. Calcd for $C_{21}H_{21}O_8N_3$: C, 56.88; H, 4.77. Found: C, 56.53; H, 4.94.

2-(2-Methyl-1-azulyl)ethyl Tosylate (2-CH_3-1-OTs). The tosylate ester of 2-CH_3-1-OH (95 mg, 0.51 mmol) was prepared in the usual way described for 1-OTs. After work-up, the ester was chromatographed on deactivated (3% H_2O) alumina[28] where CH_2Cl_2 eluted two blue bands. After solvent removal, the second band gave 38 mg of unreacted 2-CH_3-1-OH, and the first band yielded 83 mg (48%, 80% net) of unstable, blue 2-CH_3-1-OTs.

This unstable tosylate was dissolved in 0.8 ml of ethyl acetate to which had been added 57 mg (0.268 mmol) of TNB. An equal volume of hexane was added and the solution cooled to afford red-brown rosettes, mp 92.5–93.0 °C. (See paragraph at end of paper regarding supplementary material.)

Anal. Calcd for $C_{26}H_{23}O_9N_3S$: C, 56.41; H, 4.19. Found: C, 56.60; H, 4.21.

2-(2-Chloro-1-azulyl)ethanol (2-Cl-1-OH). Following the direct β-hydroxyethylation procedure described for the synthesis of 2-CH_3O-1-OAc, 255 mg (1.57 mmol) of 2-chloroazulene[12a] and 420 mg of $AlCl_3$ in 25 ml of CH_2Cl_2 at 0 °C were treated with 8 ml of a 2% solution of ethylene oxide in CH_2Cl_2. After work-up the residue was chromatographed on alumina.[28] Hexane eluted a violet band followed closely by a blue band. $CHCl_3$ developed and eluted a second blue band, and absolute ethanol removed a third blue band of unstable material that decomposed upon solvent evaporation.

The violet band afforded 150 mg of unreacted 2-chloroazulene. The first blue band yielded 5 mg (1%, 2% net) of bis(2-chloro-1-azulyl)methane which crystallized from 1:1 CCl_4–hexane to give blue, fluffy crystals: mp 193–194 °C; NMR (CCl_4, internal Me_4Si) τ 1.54–2.00 (m, 4), 2.44–3.17 (m, 8) and 5.14 (s, CH_2, 2); λ_{max} (cyclohexane) 279 nm (log ε 4.90), 292 (4.85), 335 (3.88), 351 (4.02), 364 (3.44), 573 (2.78), 615 (2.73), 670 (2.33), and 685 (2.28).

Anal. Calcd for $C_{21}H_{14}Cl_2$: C, 74.79; H, 4.18. Found: C, 75.10; H, 4.22.

The second blue band afforded 75 mg (23%, 57% net) of solid 2-Cl-1-OH: mp 32–33 °C; NMR ($CDCl_3$, internal Me_4Si) τ 1.57–2.04 (m, $C_{4,8}$ H's, 2), 2.24–3.14 (m, $C_{3,5,6,7}$ H's, 4), 6.19 [t (J = 6 Hz), α-CH_2, 2], 6.72 [t (J = 6 Hz), β-CH_2, 2], and 8.02 (s, OH, 1). For analysis a TNB complex was prepared and crystallized from 1:1 ethyl acetate–hexane to give red-brown needles: mp 95.5–96.0 °C; ir (KBr) 3.04 (m, OH) and 9.60 μ (m, C–O); λ_{max} (CH_2Cl_2) 283 nm (log ε 4.85), 291 (4.86), 304 (3.90), 324 (3.55), 334 (3.72), 348 (3.81), 565 (2.56), 600 (2.52), and 660 (2.11).

Anal. Calcd for $C_{18}H_{14}O_7N_3Cl$: C, 51.50; H, 3.36. Found: C, 51.80; H, 3.76.

2-(2-Chloro-1-azulyl)ethyl Tosylate (2-Cl-1-OTs). The tosylate ester of 2-Cl-1-OH (85 mg, 0.41 mmol) was prepared in the usual way described for 1-OTs. After work-up the ester was chromatographed on deactivated (7.4% H_2O) alumina[28] with CH_2Cl_2. The solvent was removed from the single, violet band to yield 138 mg (93%) of 2-Cl-1-OTs as a violet oil: NMR ($CDCl_3$, internal Me_4Si) τ 1.78–2.93 (m, 10), 5.73 [t (J = 7 Hz), α-CH_2, 2], 6.63 [t (J = 7 Hz), β-CH_2, 2], and 7.68 (s, tosyl CH_3, 3).

The tosylate was converted to its TNB complex. Four recrystallizations gave red-brown crystals: mp 110.0–111.5 °C; ir (KBr) 8.40 (w, S–O) and 8.50 μ (s, S–O); λ_{max} (CH_2Cl_2) 660 nm (log ε 2.09), 600 (2.51), 561 (2.55), 347 (3.76), 333 (3.64), 291 (4.79), and 282 (4.78).

Anal. Calcd for $C_{25}H_{20}O_9N_3SCl$: C, 52.32; H, 3.51. Found: C, 52.62; H, 3.44.

Diethyl 2-Bromo-1,3-azulenedicarboxylate. To 304 mg (1.06 mmol) of diethyl 2-amino-1,3-azulenedicarboxylate[1a] in 60 ml of dioxane with ice cooling and stirring was added 0.3 ml of concentrated H_2SO_4 and 250 mg (3.63 mmol) of $NaNO_2$ dissolved in 0.5 ml of water and 5 ml of dioxane. After 3–5 min the color changed from orange to green, and 0.4 ml of concentrated H_2SO_4 and 2.0 g (19.3 mmol) of NaBr in 2 ml of water were added. After an additional 5–10 min, a blue oil separated from the green solution and was visible on the flask walls. Three 250-ml portions of anhydrous ether were successively added and decanted from the mixture to precipitate and wash the diazonium salt. To this blue salt was added 100 ml of dry THF. Nitrogen evolution and a color change from blue to red was immediately observed. The mixture was allowed to stir for 30 min under cooling and filtered, the solvent volume reduced, and the residue chromatographed on alumina.[28] Benzene eluted a red band that afforded 245 mg (66%) of the title compound. Crystallization from ethanol yielded red crystals, mp 78.0–78.5 °C. (See paragraph at end of paper regarding supplementary material.)

Anal. Calcd for $C_{16}H_{15}O_4Br$: C, 54.72; H, 4.31. Found: C, 54.80; H, 4.29.

2-Bromoazulene. A solution of 240 mg (0.684 mmol) of diethyl 2-bromo-1,3-azulenedicarboxylate in 1.6 ml of ethanol and 210 mg (3.75 mmol) of potassium hydroxide in 0.4 ml of water was heated under reflux for 30 min with stirring, cooled, transferred to a centrifuge tube, acidified with 10% hydrochloric acid, washed with six 25-ml portions of water, and dried under an air stream to yield 179 mg of crude diacid.

This sample was placed in a large sublimation tube and heated to 240 °C (200 Torr). The violet sublimate that collected on the condenser was removed with hexane and chromatographed on alumina.[28] Hexane eluted a violet band that afforded 110 mg (78%) of 2-bromoazulene. Crystallization from hexane yielded violet plates: mp 104.2–104.8 °C; ir (CCl_4) no characteristic absorptions; NMR (CCl_4, internal Me_4Si) τ 1.70–1.98 (m, $C_{4,8}$ H's, 2) and 2.40–3.10 (m, 5); λ_{max} (cyclohexane) 281 nm (log ε 4.81), 289 (4.88), 303 (3.86), 332 (3.78), 346 (3.86), 359 (3.74), 557 (2.70), 596 (2.66), and 655 (2.25).

2-(2-Bromo-1-azulyl)ethyl Acetate (2-Br-1-OAc). Following the direct β-hydroxyethylation procedure described for the synthesis of 2-CH_3O-1-OAc, 400 mg (1.93 mmol) of 2-bromoazulene and 550 mg of $AlCl_3$ in 30 ml of CH_2Cl_2 at 0 °C was treated with 9.2 ml of a 2% solution of ethylene oxide in CH_2Cl_2. After 1 h, work-up gave a residue which was chromatographed on alumina[28] where CCl_4 eluted a broad, violet band of unreacted 2-bromoazulene (230 mg) followed by a blue band. Continued elution with $CHCl_3$ yielded a second blue band which afforded 175 mg (36%, 85% net) of crude 2-Br-1-OH. Absolute ethanol eluted a third blue band of unstable material that decomposed immediately after solvent removal.

The first blue band afforded 25 mg (3%, 7% net) of material identified as bis(2-bromo-1-azulyl)methane which crystallized from 1:1 $CHCl_3$–hexane as blue needles, mp 185.0–190.0 °C dec. (See paragraph at end of paper regarding supplementary material.)

The 175 mg of crude 2-Br-1-OH was acetylated with acetic anhydride in pyridine at 0°. Work-up and chromatography on alumina[28] with CH_2Cl_2 eluted a single, blue band. Solvent volume reduction and rechromatography with 3:1 CCl_4–CH_2Cl_2 afforded 165 mg

(81%) of 2-Br-1-OAc as a blue oil. (See paragraph at end of paper regarding supplementary material.)

For analysis a TNB complex was prepared and crystallized from 1:1 ethyl acetate–hexane to afford red-brown plates: mp 79.5–80.0 °C; λ_{max} (CH_2Cl_2) 285 nm (log ϵ 4.81), 295 (4.82), 334 (3.69), 349 (3.78), 361 (3.17), 566 (2.59), 605 (2.55), and 660 (2.21).

Anal. Calcd for $C_{20}H_{16}O_8N_3Br$: C, 47.45; H, 3.19. Found: C, 47.63, H, 3.33.

2-(2-Bromo-1-azulyl)ethanol (2-Br-1-OH). Basic hydrolysis of 240 mg (0.47 mmol) of 2-Br-1-OAc·TNB complex was carried out as in the synthesis of 2-CH_3O-1-OH from its acetate. After work-up, the residue was chromatographed on alumina[28] where CH_2Cl_2 developed and $CHCl_3$ eluted a blue band that yielded 108 mg (92%) of 2-Br-1-OH. (See paragraph at end of paper regarding supplementary material.)

A TNB complex was prepared and crystallized for analysis from 1:1 ethyl acetate–hexane to yield red-brown needles: mp 105.0–105.5 °C; λ_{max} (CH_2Cl_2) 285 nm (log ϵ 4.79), 295 (4.80), 335 (3.69), 349 (3.76), 362 (3.13), 568 (2.58), 605 (2.53), and 665 (2.14).

Anal. Calcd for $C_{18}H_{14}O_7N_3Br$: C, 46.57; H, 3.04. Found: C, 46.81; H, 3.27.

2-(2-Bromo-1-azulyl)ethyl Tosylate (2-Br-1-OTs). 2-Br-1-OH (105 mg, 0.43 mmol) was converted to its tosylate ester by the standard method used for 1-OTs. After work-up, the tosylate was chromatographed on deactivated (4.6% H_2O) alumina.[28] CH_2Cl_2 eluted a violet band that afforded 138 mg (81%) of 2-Br-1-OTs as a blue oil: ir (neat film) 8.35 (s, S–O) and 8.45 μ (s, S–O).

A TNB complex was produced as long, dense, dark-red needles: mp 114.0–114.5 °C. (See paragraph at end of paper regarding supplementary material.)

Anal. Calcd for $C_{25}H_{20}O_9N_3BrS$: C, 48.55; H, 3.26. Found: C, 48.67; H, 3.32.

2-(2-Iodo-1-azulyl)ethyl Acetate (2-I-1-OAc). Following the direct β-hydroxyethylation procedure described for the synthesis of 2-CH_3O-1-OAc, 475 mg (1.87 mmol) of 2-iodoazulene[12a] and 545 mg of $AlCl_3$ in 25 ml of CH_2Cl_2 at 0 °C was treated with 9.2 ml of a 2% solution of ethylene oxide in CH_2Cl_2. After 35 min, work-up gave a residue which was chromatographed on alumina.[28] CH_2Cl_2 eluted a broad, blue band that afforded 285 mg of unreacted 2-iodoazulene, and $CHCl_3$ eluted a blue band that yielded 205 mg of crude 2-I-1-OH. Absolute ethanol eluted a third, blue band that yielded 20 mg of material which was not investigated.

The 2-I-1-OH was acetylated with acetic anhydride and pyridine at 0 °C. After work-up the residue was chromatographed on alumina.[28] CCl_4–CH_2Cl_2 (1:1) eluted a broad, blue band, CH_2Cl_2 removed a diffuse, blue band, and $CHCl_3$ eluted a narrow, blue band. Only the first blue band was investigated and afforded 160 mg (25%, 63% net) of 2-I-1-OAc. Crystallization from hexane afforded blue rosettes, mp 69.0–69.5 °C. (See paragraph at end regarding supplementary material.)

Anal. Calcd for $C_{14}H_{13}O_2I$: C, 49.43; H, 3.85. Found: C, 49.56; H, 3.90.

2-(2-Cyano-1-azulyl)ethyl Acetate (2-CN-1-OAc). A mixture of 137 mg (0.40 mmol) of 2-I-1-OAc and 53 mg (0.60 mmol) of CuCN in 10 ml of dry DMF was heated at 150 °C with stirring for 2 h. The color of this mixture changed during this period from blue to blue-brown. The mixture was cooled, diluted with 100 ml of benzene, and washed with six 100-ml porions of warm, aqueous NaCN (prepared from 600 ml of warm water and 20 g of NaCN). The organic layer was washed with water and dried (Na_2SO_4), the solvent volume reduced, and the residue chromatographed on alumina.[28] CCl_4–CH_2Cl_2 (1:1) eluted a violet band, CH_2Cl_2 eluted a broad, blue band, anhydrous ether eluted a blue-green band, and $CHCl_3$ eluted a violet and a green-blue band. The broad, blue band afforded 83 mg (86%) of 2-CN-1-OAc. The other bands were not investigated. The product acetate was isolated as a blue-green oil. (See paragraph at end of paper regarding supplementary material.)

For analysis a TNB complex was prepared and crystallized from 1:1 ethyl acetate–hexane. Recrystallization yielded green spherulites: mp 96.6–97.5 °C; λ_{max} (CH_2Cl_2) 256 nm (log ϵ 4.47) (sh), 289 (4.69), 300 (4.64), 334 (3.78), 342 (3.75), 347 (3.81), 357 (3.48), 606 (2.69), 648 (2.70), and 710 (2.45) (sh).

Anal. Calcd for $C_{21}H_{16}O_8N_4$: C, 55.75; H, 3.57. Found: C, 55.98; H, 3.73.

2-(2-Cyano-1-azulyl)ethanol (2-CN-1-OH). Basic hydrolysis of 210 mg (0.88 mmol) of 2-CN-1-OAc was carried out as in the synthesis of 2-CH_3O-1-OH from its acetate. After work-up the residue was chromatographed on alumina[28] where $CHCl_3$ eluted a single, blue band that yielded 170 mg (99%) of the title compound. Crystallization from 1:1 ether–hexanes afforded green needles, mp 50.0–50.5 °C. (See paragraph at end of paper regarding supplementary material.)

Anal. Calcd for $C_{13}H_{11}ON$: C, 79.16; H, 5.62. Found: C, 79.29; H, 5.64.

2-(2-Cyano-1-azulyl)ethyl Tosylate (2-CN-1-OTs). 2-CN-1-OH (140 mg, 0.71 mmol) was converted to its tosylate ester by the standard method used for 1-OTs. After work-up, the tosylate was chromatographed on deactivated (4.6% H_2O) alumina with CH_2Cl_2. A blue band was eluted which afforded 235 mg (94%) of the title compound which was crystallized from CH_2Cl_2 and hexane as long, dense, green needles, mp 109.2–110.0 °C. (See paragraph at end of paper regarding supplementary material.)

Anal. Calcd for $C_{20}H_{17}O_3SN$: C, 68.35; H, 4.88. Found: C, 68.46; H, 4.96.

Diethyl 6-Bromo-1,3-azulenedicarboxylate (7). To a 2.00 g (5.46 mmol) of diethyl 2-amino-6-bromo-1,3-azulenedicarboxylate (**6**)[12a] in 350 ml of dioxane was added 535 mg of concentrated sulfuric acid in 10 ml of tetrahydrofuran and 600 mg (5.45 mmol) of *p*-hydroquinone. In two addition funnels were placed separately 11.20 g (102 mmol) of *p*-hydroquinone in 200 ml of dioxane and 12.5 g (107 mmol) of isoamyl nitrite in 200 ml of dioxane. The contents of the two addition funnels were added simultaneously at approximately equal rates at room temperature to the stirred solution as the color changed from orange to red. This mixture was stirred for 3 h, diluted with 500 ml of 1 M aqueous sodium sulfite, and extracted with three 500-ml portions of hexane. The combined extracts were washed with two 500-ml portions of water and dried (Na_2SO_4), and the solvent volume reduced. The residue was chromatographed on alumina.[28] Benzene eluted a red band and developed a yellow band that was eluted with CH_2Cl_2. The yellow band afforded 80 mg of unreacted **6** and the red band gave 1.791 g (93%, 97% net) of **7**. Crystallization from benzene yielded dark, red needles, mp 206.0–207.5 °C (lit.[12a] 26%, mp 206–207 °C). (See paragraph at end of paper regarding supplementary material.)

Anal. Calcd for $C_{16}H_{15}O_4Br$: C, 54.72; H, 4.31. Found: C, 54.70; H, 4.53.

Dimethyl 6-Methoxy-1,3-azulenedicarboxylate (12). To 125 ml of methanol [distilled from $Mg(OCH_3)_2$] was added 253 mg (11.0 mg-atoms) of sodium. After the sodium had dissolved, 1.00 g (2.73 mmol) of **7** was added with stirring and the solution was heated under reflux for 3 h with a gradual color change from red to orange. The methanol was removed on a rotary evaporator and the residue was chromatographed on alumina.[28] Benzene developed a small red band in front of the large orange band and the red band was collected to yield 40 mg of **7** by analysis of the NMR spectrum. The major portion of the orange band was eluted with CH_2Cl_2 to give 640 mg (82%, 85.5% net) of **12**. Crystallization of this product from benzene gave orange needles, mp 149–150.2 °C. (See paragraph at end of paper regarding supplementary material.)

6-Methoxyazulene (17). When 640 mg (2.34 mmol) of **12** was dissolved in 80 ml of concentrated H_2SO_4, a yellow solution resulted. After stirring for 2 h at 25 °C, no color change was noted. This solution was poured slowly into 800 ml of ice water with stirring with the immediate formation of an orange-yellow precipitate. This solid was collected by centrifugation and washed with eight 30-ml portions of water. After drying (12 h, 50 °C), 555 mg (96.5%) of 6-methoxy-1,3-azulenedicarboxylic acid was obtained: NMR (Me_2SO-d_6, internal Me_4Si) τ −2.30 (broad s, CO_2H, 2), 0.36 [d (J = 11.5 Hz), $C_{4,8}$ H's, 2], 1.62 (s, C_2 H, 1), 2.44 [d (J = 11.5 Hz), $C_{5,7}$ H's, 2], and 5.92 (s, OCH_3, 3).

This sample was placed in a large sublimation tube and heated to 240–250 °C (160 Torr) for 8 h. During this time, violet plates formed on the condenser and were removed periodically. This product was chromatographed on alumina with 9:1 hexane–CH_2Cl_2 to yield, after solvent evaporation, 247 mg (67% based on starting diester) of **17**: mp 113–113.5 °C (lit.[30] 112–113 °C); ir (KBr) 6.30 (m), 9.90 (m), 12.07 (s). and 13.39 μ (s); NMR (CCl_4, internal Me_4Si) τ 1.91 [d (J = 10.5 Hz), $C_{4,8}$ H's, 2], 2.46 [t (J = 4.0 Hz), C_2 H, 1], 2.83 [d (J = 4.0 Hz), $C_{1,3}$ H's, 2], 3.34 [d(J = 10.5 Hz), $C_{5,7}$ H's, 2], and 6.13 (s, OCH_3, 3); λ_{max} (cyclohexane) 635 nm (log ϵ 1.80), 605 (1.93), 579 (3.34), 551 (2.29), 533 (2.34), 514 (2.28), 366 (3.48), 353 (3.67), 344 (3.59), 338 (3.58), 330 (3.51), 310 (3.93), 293 (4.82), 287 (4.80), and 282 (4.77).

Anal. Calcd for $C_{11}H_{10}O$: C, 83.51; H, 6.37. Found: C, 83.70; H, 6.51.

2-(6-Methoxy-1-azulyl)ethyl Tosylate (6-CH_3O-1-OTs). 6-CH_3O-1-OH[5] (135 mg, 0.67 mmol) was converted to its tosylate

ester under the conditions used for 1-OTs. Work-up and chromatography on deactivated (4% H_2O) alumina[28] with CH_2Cl_2 gave 238 mg (80%) of 6-CH_3O-1-OTs as an unstable violet-red oil: ir (neat film) 6.32 (s), 8.34 (s, S–O), and 8.47 μ (s, S–O); NMR ($CDCl_3$, internal Me_4Si) τ 1.80–3.40 (m, 10), 5.71 [t (J = 7.0 Hz), α-CH_2, 2], 6.12 (s, OCH_3, 3), 6.65 [t (J = 7.0 Hz), β-CH_2, 2], and 7.65 (s, CH_3, 3).

The product was converted to the TNB complex, which would not crystallize from ethyl acetate–hexane. However, upon standing at freezer temperature (−27 °C) for 1 week, a brown solid resulted, which softened at room temperature to a semisolid. Repeated attempts to purify this sample by recrystallization or chromatography did not yield a crystalline compound, but gave a solid with each cooling at freezer temperature which partially melted at room temperature. This complex was unstable at room temperature in the presence of air or in CH_2Cl_2 solution at room temperature over a 2-day period: λ_{max} (CH_2Cl_2) 539 nm (log ϵ 2.40), 370 (3.21), 357 (3.70), 350 (3.62), 342 (3.59), 297 (4.76), and 291 (4.76).

2-(6-Methyl-1-azulyl)ethyl Tosylate (6-CH_3-1-OTs). 6-CH_3-1-OH[5] (115 mg, 0.62 mmol) was converted to its tosylate ester by the method used for 1-OTs. Work-up and chromatography on deactivated (6% H_2O) alumina[28] with CH_2Cl_2 eluted two blue bands. After solvent removal, the first, blue band afforded 174 mg (83%) of 6-CH_3-1-OTs and the second band gave 20 mg of unreacted 6-CH_3-1-OH.

The tosylate ester was converted to its TNB complex as clusters of red-brown needles, mp 99.0–99.5 °C. (See paragraph at end of paper regarding supplementary material.)

Anal. Calcd for $C_{26}H_{23}N_3O_9S$: C, 56.41; H, 4.18. Found: C, 56.80; H, 4.02.

2-(6-Methyl-1-azulyl)ethyl Acetate (6-CH_3-1-OAc). 6-CH_3-1-OH (74 mg, 0.40 mmol) was acetylated with acetic anhydride in pyridine at 0 °C. Work-up and chromatography on alumina[28] gave 63 mg (75%) of the acetate (CH_2Cl_2 eluent) as a blue oil. This was converted to its TNB complex as long, violet-brown needles from ethyl acetate–hexane, mp 104.8–105.1 °C. (See paragraph at end of paper regarding supplementary material.)

Anal. Calcd for $C_{21}H_{19}N_3O_8$: C, 57.14; H, 4.34. Found: C, 57.37; H, 5.23.

6-Bromoazulene (16). Diethyl 6-bromo-1,3-azulenedicarboxylate (7, 500 mg, 1.42 mmol) was dissolved in 20 ml of concentrated H_2SO_4 and the resultant yellow solution stirred for 2 h at room temperature. This solution was poured into 200 ml of ice water with an instantaneous formation of a finely divided red solid. The precipitate was collected by centrifugation and the gelatinous precipitate washed with ten 15-ml portions of water. The product was collected and dried (70 °C, 4 h) to yield 402 mg (96%) of 6-bromo-1,3-azulenedicarboxylic acid, which was finely ground and placed in a large sublimation tube. Upon heating to 230 °C (200 Torr) a blue solid appeared on the condenser. Heating was maintained for 10 h with periodic removal of the product from the condenser. Chromatography of this compound on alumina[28] with 9:1 hexane–CH_2Cl_2 yielded 133 mg (47%, 45% based on starting ester) of **16**: mp 106.5–108.0 °C; ir (KBr) 10.49 (m), 12.11 (s), and 13.28 μ (m); NMR (CCl_4, internal Me_4Si) τ 1.92–2.21 (m, 3) and 2.46–2.70 (m, 4); λ_{max} (cyclohexane) 702 nm (log ϵ 2.13), 662 (2.14), 636 (2.46), 607 (2.45), 582 (2.49), 560 (2.41), 539 (2.32), 521 (2.17), 362 (3.13), 347 (3.77), 340 (3.58), 334 (3.63), 304 (3.80), 288 (4.90), 282 (4.85), and 278 (4.81). A sublimed sample, mp 104.5–105.0°, was submitted for analysis.

Anal. Calcd for $C_{10}H_7Br$: C, 57.99; H, 3.41. Found: C, 58.10; H, 3.65.

2-(6-Bromo-1-azulyl)ethyl Tosylate (6-Br-1-OTs). 6-Br-1-OH[5] (24 mg, 0.096 mmol) was converted to its tosylate ester under the conditions outlined for 1-OTs. Isolation and purification of the product gave 32 mg (82%) of 6-Br-1-OTs as silky blue needles, mp 92.2–93.0 °C. (See paragraph at end of paper regarding supplementary material.)

Anal. Calcd for $C_{19}H_{17}O_3SBr$: C, 56.31; H, 4.23. Found: C, 56.37; H, 4.36.

2-(6-Cyano-1-azulyl)ethyl Acetate (6-CN-1-OAc). 6-Br-1-OAc (180 mg, 0.62 mmol) (produced by Ac_2O–pyridine acetylation of 6-Br-1-OH) and 83 mg (0.93 mmol) of CuCN in 10 ml of dry DMF was heated for 6.5 h at 135 °C with stirring under an N_2 atmosphere. Work-up (see synthesis of 2-CN-1-OAc) and chromatography on alumina[28] with CH_2Cl_2 first eluted 30 mg of unreacted 6-Br-1-OAc. This was followed by a blue band containing 100 mg (68%) of 6-CN-1-OAc as a green oil: ir (neat film) 4.52 (m, C≡N), 5.75 (s, C=O), and 9.60 μ (s, C–O); NMR (CCl_4, internal Me_4Si) τ 1.73–2.97 (m, 6), 5.73 [t (J = 7 Hz), α-CH_2, 2], 6.68 [t (J = 7 Hz), β-CH_2, 2], and 8.03 (s, CH_3, 3).

For analysis a TNB complex was prepared and crystallized from 1:1 ethyl acetate–hexane to yield green plates: mp 80.0–80.5 °C; λ_{max} (CH_2Cl_2) 280 nm (log ϵ 4.88) (sh), 290 (5.07), 306 (3.95) (sh), 337 (3.80), 354 (3.88), 654 (2.53), and 722 (2.46).

Anal. Calcd for $C_{21}H_{16}O_8N_4$: C, 55.75; H, 3.57. Found: 55.72; H, 3.53.

2-(6-Cyano-1-azulyl)ethanol (6-CN-1-OH). Basic hydrolysis of 110 mg (0.46 mmol) of 6-CN-1-OAc was carried out as in the synthesis of 2-CH_3O-1-OH from its acetate. After work-up, the green residue was chromatographed on alumina[28] where $CHCl_3$ eluted a single, light-blue band that yielded 90 mg (100%) of 6-CN-1-OH as a green oil: ir (neat film) 3.00 (s, OH), 4.55 (s, CN), and 9.60 μ (s, C–O); NMR ($CDCl_3$, internal Me_4Si) τ 1.73–2.97 (m, 6), 6.12 [t (J = 6 Hz), α-CH_2, 2], 6.75 [t (J = 6 Hz), β-CH_2, 2], and 7.42 (s, OH, 1).

For analysis a TNB complex was prepared and crystallized from 1:1 ethyl acetate–hexane to give light-brown needles: mp 77–78 °C; λ_{max} (CH_2Cl_2) 281 nm (log ϵ 4.85) (sh), 290 (5.03), 338 (3.68), 353 (3.80), 657 (2.53), and 725 (2.44).

Anal. Calcd for $C_{19}H_{14}O_7N_4$: C, 55.61; H, 3.44. Found: C, 55.54; H, 3.28.

2-(6-Cyano-1-azulyl)ethyl Tosylate (6-CN-1-OTs). 6-CN-1-OH (90 mg, 0.46 mmol) was converted to its tosylate ester under conditions as in the synthesis of 1-OTs. Work-up gave a green residue which was chromatographed on deactivated (6% H_2O) alumina[28] where CH_2Cl_2 eluted two blue bands. The second band contained 10 mg of unreacted 6-CN-1-OH while the first band afforded 125 mg (78%) of 6-CN-1-OTs. The tosylate was crystallized from 1.5 ml of 1:1 ethyl acetate–hexane to afford green crystals, mp 118.0–119.5 °C. (See paragraph at end of paper regarding supplementary material.)

Anal. Calcd for $C_{20}H_{17}O_3NS$: C, 68.35; H, 4.88. Found: C, 68.26; H, 4.98.

6-Cyanoazulene. To 60 mg (0.29 mmol) of 6-bromoazulene was added 4 ml of dry DMF and 34 mg (0.38 mmol) of CuCN. The mixture was heated to 150 °C and maintained at this temperature for 6 h with stirring. The cooled mixture was diluted with 50 ml of benzene and the benzene layer was shaken vigorously with three portions of warm, concentrated aqueous NaCN solution. The organic layer was then washed with water and dried (Na_2SO_4), and the solvent volume reduced. The concentrated green benzene solution was chromatographed on alumina.[28] Benzene developed a blue band which was eluted with 1:1 hexane–CH_2Cl_2 to yield, after solvent removal, 35 mg (78%) of 6-cyanoazulene: mp 51–52 °C; ir (film) 4.52 (m, C≡N), 11.97 (s), 12.82 (s), and 13.21 μ (s); NMR (CCl_4, internal Me_4Si) τ 1.64 [d (J = 10.0 Hz), $C_{4,8}$ H's, 2], 1.90 [t (J = 4.0 Hz), C_2H, 1], 2.46 [d (J = 4.0 Hz), $C_{1,3}$ H's, 2], and 2.59 [d (J = 10.0 Hz), $C_{5,7}$ H's, 2]; λ_{max} (cyclohexane) 774 nm (log ϵ 1.96), 721 (2.20), 696 (2.54), 660 (2.51), 631 (2.57), 606 (2.48), 584 (2.40), 362 (3.70), 346 (3.82), 333 (3.65), and 283 (4.01).

Anal. Calcd for $C_{11}H_7N$: C, 86.24; H, 4.61. Found: C, 86.20; H, 4.81.

Diethyl 2-Nitroaminoazulene-1,3-dicarboxylate (21). Diethyl 2-amino-1,3-azulenedicarboxylate (**3**,[1a] 500 mg, 1.74 mmol) was dissolved in 15 ml of acetic anhydride and the orange solution was chilled in a dry ice–2-propanol bath. To the cold solution was added 521 mg (2.16 mmol) of $Cu(NO_3)_2$-$(H_2O)_3$ dissolved in 25 ml of acetic anhydride over a 10-min period with stirring, resulting in a green solution. The solution was allowed to warm to room temperature, the color changing to brown. The solution was diluted with cold water and extracted with CH_2Cl_2. The CH_2Cl_2 was extracted three times with dilute NH_4OH, imparting an orange-red color to the NH_4OH layer. The CH_2Cl_2 layer was washed with water and dried ($MgSO_4$), and the solvent evaporated. The residue was chromatographed on basic alumina with CH_2Cl_2 to yield, after evaporation of solvent, 224 mg of starting **3**.

The NH_4OH extracts were combined, neutralized with 5% hydrochloric acid, and extracted with CH_2Cl_2. The red organic layer was washed with water and dried ($MgSO_4$), and the solvent volume reduced to give 233 mg (40.3%, 73% net yield) of **21**. An analytical sample was prepared by recrystallization from a minimum amount of CH_2Cl_2 affording large, orange-red needles, mp 147–149 °C. (See paragraph at end of paper regarding supplementary material.)

Anal. Calcd for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.86. Found: C, 57.71; H, 5.03.

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Registry No.—1-OH, 26157-06-2; 3-CH_3O-1-OH, 58311-89-0; 3-CH_3O-1-OH TNB complex, 58311-90-3; 3-CH_3-1-OH, 58311-91-4; 3-CH_3-1-OH TNB complex, 58311-92-5; 3-CH_3S-1-OH, 58311-93-6; 3-Br-1-OH, 58311-94-7; 3-CH_3CO-1-OH, 58311-95-8; 3-CN-1-OH, 58311-96-9; 3-CN-1-OH 2TNB complex, 58311-97-0; 3-NO_2-1-OH, 26157-07-3; 3-NO_2-1-OH α-naphthyl urethane, 58311-98-1; 2-CH_3O-1-OH, 58311-99-2; 2-CH_3O-1-OH TNB complex, 58312-00-8; 2-CH_3-1-OH, 58312-01-9; 2-CH_3-1-OH TNB complex, 58312-02-0; 2-Cl-1-OH, 58343-23-0; 2-Cl-1-OH TNB complex, 58343-24-1; 2-Br-1-OH, 58312-03-1; 2-Br-1-OH TNB complex, 58312-04-2; 2-I-1-OH, 58312-05-3; 2-CN-1-OH, 58312-06-4; 6-CH_3O-1-OH, 35046-06-1; 6-Br-1-OH, 35096-49-2; 6-CN-1-OH, 58312-07-5; 6-CN-1-OH TNB complex, 58312-08-6; 1-OAc, 26154-65-4; 1-OAc TNB complex, 58312-09-7; 3-SCN-1-OAc, 58312-10-0; 3-CH_3S-1-OAc, 58312-11-1; 3-CH_3S-1-OAc TNB complex, 58312-12-2; 3-Br-1-OAc, 58312-13-3; 3-Br-1-OAc TNB complex, 58312-14-4; 3-CH_3CO-1-OAc, 58312-15-5; 3-CH_3CO-1-OAc TNB complex, 58312-16-6; 3-CN-1-OAc, 58312-17-7; 3-NO_2-1-OAc, 58312-18-8; 2-CH_3O-1-OAc, 58312-19-9; 2-CH_3O-1-OAc TNB complex, 58312-20-2; 2-Br-1-OAc, 58312-21-3; 2-Br-1-OAc TNB complex, 58312-22-4; 2-I-1-OAc, 58312-23-5; 2-CN-1-OAc, 58312-24-6; 2-CN-1-OAc TNB complex, 58312-25-7; 6-CH_3-1-OAc, 58312-26-8; 6-CH_3-1-OAc TNB complex, 58312-27-9; 6-CN-1-OAc, 58312-28-0; 6-CN-1-OAc TNB complex, 58312-29-1; 6-Br-1-OAc, 58312-30-4; 1-OTs, 26154-60-9; 1-OTs TNB complex, 58312-31-5; 3-CH_3O-1-OTs, 58312-32-6; 3-CH_3O-1-OTs TNB complex, 58312-33-7; 3-CH_3-1-OTs, 58312-34-8; 3-CH_3-1-OTs TNB complex, 58312-35-9; 3-CH_3S-1-OTs, 33318-68-2; 3-CH_3S-1-OTs TNB complex, 58312-36-0; 3-Br-1-OTs, 33318-67-1; 3-Br-1-OTs TNB complex, 58312-37-1; 3-CH_3CO-1-OTs, 26154-62-1; 3-CN-1-OTs, 58312-38-2; 3-NO_2-1-OTs, 26154-61-0; 2-CH_3O-1-OTs, 58312-39-3; 2-CH_3O-1-OTs TNB complex, 58312-40-6; 2-CH_3-1-OTs, 58312-41-7; 2-CH_3-1-OTs TNB complex, 58312-42-8; 2-Cl-1-OTs, 58312-43-9; 2-Cl-1-OTs TNB complex, 58312-44-0; 2-Br-1-OTs, 58312-45-1; 2-Br-1-OTs TNB complex, 58312-46-2; 2-CN-1-OTs, 58312-47-3; 6-CH_3O-1-OTs, 58312-48-4; 6-CH_3O-1-OTs TNB complex, 58312-49-5; 6-CH_3-1-OTs, 58312-50-8; 6-CH_3-1-OTs TNB complex, 58312-51-9; 6-Br-1-OTs, 58312-52-0; 6-CN-1-OTs, 58312-53-1; **3**, 3806-02-8; **4** (R = CH_3; X = CH_3O), 734-61-2; **4** (R = C_2H_5; X = Cl), 36044-40-3; **4** (R = C_2H_5; X - Br), 58312-54-2; **4** (R = H; X = Br), 58312-55-3; **5** (X = CH_3O), 36044-37-8; **5** (X = CH_3), 769-86-8; **5** (X = CH_3) TNB complex, 58312-56-4; **5** (X = Cl), 36044-31-2; **5** (X = Br), 58312-57-5; **5** (X = I), 36044-41-4; **6**, 50469-71-1; **7**, 1157-45-5; **10** (R = H; X = CH_3O), 58312-58-6; **10** (R = H; X = Br), 33828-73-8; **12**, 53535-54-9; **16**, 35046-05-0; **17**, 35046-03-8; **21**, 58312-59-7; 1-azulylmethyltrimethylammonium idoide, 40450-20-2; 1-azulylacetonitrile, 53271-95-7; 1-azulylacetic acid, 26157-12-0; *p*-toluenesulfonyl chloride, 98-59-9; 1-azulyl benzoate, 58312-60-0; azulene, 275-51-4; benzoyl peroxide, 94-36-0; 1,3-azulene dibenzoate, 58312-61-1; 1-methoxyazulene, 30264-97-2; 1-methoxyazulene TNB complex, 58312-62-2; *N,N,N',N'*-tetramethyldiaminomethane, 51-80-9; (3-methoxy-1-azulylmethyl)trimethylammonium iodide, 58312-63-3; 3-methoxy-1-azulylacetonitrile, 58312-64-4; 3-methoxy-1-azulylacetic acid, 58312-65-5; (3-methyl-1-azulylmethyl)trimethylammonium iodide, 58312-66-6; tetranitromethane, 509-14-8; 1,3-bis(2-hydroxyethyl)-2-methylazulene, 58312-67-7; 1,3-bis(2-hydroxyethyl)-2-methylazulene TNB complex, 58312-68-8; bis(2-chloro-1-azulyl)methane, 58312-69-9; bis(2-bromo-1-azulyl)methane, 58312-70-2; 6-cyanoazulene, 58312-71-3.

Supplementary Material Available. Principal ir, full NMR, and uv-visible data for the compounds so designated (9 pages). Ordering information is given on any current masthead page.

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Nonbenzenoid Aromatic Systems. XIII.[1a] Certain Substituent Group Effects on the pK_a of 1-Azulenecarboxylic Acid

Richard N. McDonald,* R. R. Reitz,[1b] and James M. Richmond

Department of Chemistry, Kansas State University, Manhattan, Kansas 66506

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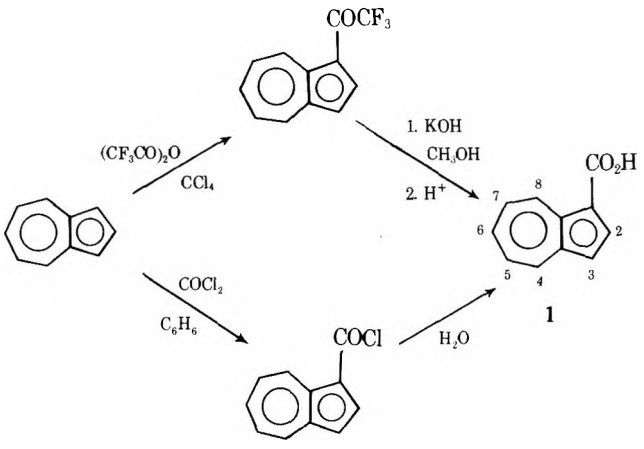
The synthesis of 2- (OCH_3, CH_3, Cl, Br, I, CN), 3- (OCH_3, CH_3, Br, $COCH_3$, CN, NO_2) and 6-substituted (OCH_3, CH_3, Br) 1-azulenecarboxylic acids (1) as well as 4-, 5- and 7-CH_3-1's are described. The thermodynamic pK_a's of these derivatives of 1 (except for 2-I-1 and 2-CN-1 owing to poor solubility) were determined in 50% (v/v) aqueous ethanol at 25.0 °C. The four substituent effects in the ortholike 2 position of 1 are correlated with σ_p^0 constants. Compared to related effects in o-$XC_6H_4CO_2H$ ionizations, a significant steric contribution to the ortho effect in the ortho-substituted benzoic acid derivatives is clearly established. The six substituent effects in 3-X-1 pK_a's show that the 3 position in 1 behaves intermediate between a benzene meta and para position. The variable behavior of substituent effects at the 3 position relative to the nature of the reaction center at C_1 is discussed. The limited 6-X-1 data set is in keeping with this position being a long-range paralike position. The individual methyl group effects at positions C_4–C_7 of the seven-membered ring are correlated with results of CNDO/2 calculations on 1 and its conjugate base. Although a small alternating effect is observed at C_4–C_7, the methyl group effects center around σ_p^0 behavior.

Hammett's choice of the dissociation of substituted benzoic acids in water at 25 °C as the standard reaction (ρ = 1.0) in developing his classic $\rho\sigma$ linear free energy relationship placed the study of substituent effects on aromatic carboxylic acid pK_a's at center stage in such correlation analyses.[2] As we approach the general question of how substituent effects are felt and transmitted from various nonequivalent positions to attached reaction centers in azulene, it was fitting and proper to initiate this general study by determining the effects of substituent groups on the pK_a's of the azulenecarboxylic acids.[3] The present paper will deal with certain substituent effects at the 2 (benzene ortholike), 3 (benzene metalike), and 6 positions (long-range benzene paralike) as well as the methyl group effects at the 2–7 positions on the pK_a of 1-azulenecarboxylic acid (1) in 50% (v/v) aqueous ethanol at 25 °C.

Synthesis of Substituted 1-Azuloic Acids. Two convenient methods are available for introducing the carboxylic acid group into the 1 position of azulene: (1) trifluoroacetylation of azulene using trifluoroacetic anhydride followed by base hydrolysis,[4] and (2) reaction of azulene with phosgene followed by hydrolysis.[5]



3-Substituted 1-Azuloic Acids (3-X-1). The acids 3-X-1 where X = Br, $COCH_3$, CN, and NO_2 were prepared by electrophilic substitution in the 3 position of methyl 1-azulenecarboxylate[4] followed by base hydrolysis to the respective acids. For the substituents X = CH_3O and CH_3, 1-methoxy-[1a] and 1-methylazulene[1a] were trifluoroacetylated. Base hydrolysis of 3-methyl-1-trifluoroacetylazulene gave 3-CH_3-1 while base hydrolysis of 3-methoxy-1-trifluoroacetylazulene led to extensive decomposition. However, 3-CH_3O-1 was prepared by treating 1-methoxyazulene with phosgene followed by hydrolysis.

2-Substituted 1-Azuloic Acids (2-X-1). Using Anderson's trifluoroacetylation procedure,[4] 2-methoxy-, 2-methyl-, 2-chloro, 2-bromo-, and 2-iodoazulenes[1a] were converted to the corresponding 2-X-1's. The synthesis of 2-CN-1 involved conversion of 2-I-1 to methyl 2-iodo-1-azulenecarboxylate (2) followed by reaction of **2** with cuprous cyanide in refluxing dimethylformamide (DMF). Hydrolysis of the methyl ester gave 2-CN-1.

6-Substituted 1-Azuloic Acids (6-X-1). 6-Methoxyazulene[1a] was allowed to react with phosgene and hydrolysis of the product acid chloride gave 6-CH_3O-1. Base hydrolysis of methyl 6-methyl-1-azulenecarboxylate[6] produced 6-CH_3-1.

6-Bromoazulene[1a] was converted to 6-Br-1 by reaction with phosgene and then hydrolysis. Since the sample of 6-Br-1 failed to give a satisfactory elemental analysis, it was converted to the methyl ester with diazomethane. Halogenodealkylation of methyl 6-bromo-1-azulenecarboxylate with lithium bromide in refluxing DMF afforded 6-Br-1 (46%) and 6-bromoazulene (39%). Here again a satisfactory elemental analysis was not obtained with 6-Br-1.

4-, 5-, and 7-Methyl-1-azuloic Acids. Trifluoroacetylation of 4-methylazulene[7] produced a single product identified as 1-trifluoroacetyl-4-methylazulene (3), on the basis of its NMR spectrum. The presence of the trifluoroacetyl group at C_1 has a marked anisotropic effect on the peri-C_8H if this proton is present; in the case of **3** this effect was apparent. Base hydrolysis of **3** gave 4-CH_3-1.

When a mixture of methyl 5- (4) and 7-methyl-1-azulenecarboxylates (5)[6] was chromatographed on Woelm alumina, the two isomers were separated. Each ester was then hydrolyzed to the corresponding acid. Their structural assignments are based on the NMR spectra of the methyl esters. In **4** the peri-C_8H is coupled to C_7H while in **5** this coupling is absent.

pK_a's of Substituted 1-Azuloic Acids. The thermodynamic pK_a's of the substituted 1-azuloic acids were determined in 50% (v/v) aqueous ethanol at 25 °C[3] and are listed in Table I. Even in this solvent the low solubilities of 2-CN-1 and 2-I-1 precluded their pK_a determinations.

Although the data sets for 2-X-1 and 6-X-1 are quite limited, the 3-X-1 data set contains a reasonable number of substituent groups and spread in their electronic responses to a reaction center. The present collection of pK_a data

Table I. pK_a's of Substituted 1-Azuloic Acids in 50% (v/v) Aqueous Ethanol at 25.00 ± 0.01 °C

Registry no.	Substituent in X-1	pK_a	ΔpK_a [pK_a (H) − pK_a (X)]
1201-25-8	H	6.992 ± 0.004[a]	0.000
58313-00-1	2-CH_3O	7.296 ± 0.004	−0.304
33447-31-3	2-CH_3	7.311 ± 0.006	−0.319
54798-17-3	2-Cl	6.422 ± 0.013	0.570
58313-01-2	2-Br	6.392 ± 0.008	0.600
58313-02-3	3-CH_3O	6.952 ± 0.006	0.040
58313-03-4	3-CH_3	7.092 ± 0.007	−0.100
58313-04-5	3-Br	6.528 ± 0.017	0.464
58313-05-6	3-CH_3CO	6.208 ± 0.014	0.784
58313-06-7	3-CN	5.898 ± 0.012	1.094
31802-33-2	3-NO_2	5.612 ± 0.011	1.380
10527-10-3	4-CH_3	7.096 ± 0.007	−0.104
58313-07-8	5-CH_3	7.192 ± 0.004	−0.200
58313-08-9	6-CH_3O	7.154 ± 0.010	−0.162
58313-09-0	6-CH_3	7.118 ± 0.003	−0.126
58313-10-3	6-Br	6.616 ± 0.023	0.376
58313-11-4	7-CH_3	7.171 ± 0.005	−0.179

[a] Standard deviations.

should minimally answer the question of how the 3 substituents interact with the reaction centers involved in the carboxylic acid–carboxylate anion equilibrium; that is, relative to the 1 position is the 3 position a "benzene metalike" position?

To answer this question, the pK_a data in Table I were treated by regression analysis and these results are listed in Table II. Our analysis began by treating each data set with the Yukawa–Tsuno–Sawada (YTS) relationship[8] treating each position as paralike in the expression $\Delta pK_a = \rho[\sigma_p^0 + r(\sigma_p^+ - \sigma_p^0)]$.[8]

It was immediately obvious from the results of the YTS correlations that from the small values of r, σ_p^0 constants correlated the limited 2-X-1 and 6-X-1 data sets. However, the value of $r = -0.18$ for the 3-X-1 data set indicated that less resonance than that present in σ_p^0 constants[8b] was involved in the interaction of the 3 substituents and the C_1 acid function. That σ_m and σ_m^0 constants appear to overcorrect this is shown in those correlations in Table II. Figure 1 shows the pK_a data plotted against σ_p^0 constants.

The reduced resonance effect by 3 substituents compared to that predicted by σ_p^0 constants is seen with *both* the 3-CH_3O-1[9] and 3-CH_3-1 acid pK_a's compared to the correlation line using 1 and the four 3-X-1's bearing electron-withdrawing groups. A further check on this point was carried out using the Swain–Lupton correlation, $\Delta pK_a = f\mathcal{F} + r\mathcal{R} + i$;[10] see Table III. The $\%\mathcal{R}$ (average relative importance of resonance) was 37 ± 4, which may be compared with 53% for σ_p, 22% for σ_m, 42% for σ_p^0, and 23% for σ_m^0.[10] Thus both the YTS and Swain–Lupton dual substituent approaches lead to the same conclusion that the 3 position in 3-X-1's behaves intermediate between a meta and para position in benzene derivatives.

Roberts et al.[12] reported $\rho = 1.46 \pm 0.05$ for *m*- and *p*-$XC_6H_4CO_2H$ ionization in 50% aqueous ethanol using Hammett σ constants. As we can see from the data for 3-X-1 and 6-X-1 pK_a's quite similar ρ values are obtained for the 1-azulenecarboxylic acid ionization using a somewhat different σ (σ_p^0) constant. Although this agreement in ρ values is excellent comparing the substituted benzoic acids with the combined 3-X-1's and 6-X-1's (last entry in Table II), there may be some doubt concerning the validity in the combination of these two data sets. This corroborates the position taken by Dewar et al.[13] and modified by Forsyth[14] in using the ρ value determined for benzene derivatives and "synthesizing" σ's for correlating substituent effects in other aryl units in related reaction processes.

Table II. Regression Analysis of Substituted 1-Azuloic Acids pK_a Data

Position (parameter)[a,g]	ρ	r[b]	C[c]	s[d]	F[e]	n[f]
2 (YTS)	2.15 ± 0.05	0.4	1.000	0.02	1232	5
3 (YTS)	1.68 ± 0.06	−0.18	0.998	0.04	586	7
6 (YTS)	1.22 ± 0.09	0.05	0.998	0.03	119	4
3 (σ_m)	1.93 ± 0.20		0.975	0.14	97	7
3 (σ_m^0)	1.87 ± 0.17		0.979	0.13	115	7
3 (σ_p^0)	1.52 ± 0.09		0.991	0.09	263	7
3 (σ_p^0), 6 (σ_p^0)	1.45 ± 0.07		0.989	0.09	350	10

[a] Position(s) and constant(s) used in correlation. Yukawa–Tsuno–Sawada identified as YTS. [b] The value of r in YTS equation. [c] Correlation coefficients. [d] Standard error of the estimate in pK_a units. [e] Critical value of the variance ratio test. [f] Number of points in data set; each uses X = H. [g] The sources for the substituent constants used in these analyses were σ_m (ref 10), σ_p (ref 10), σ_m^0 (ref 8b), and σ_p^0 (ref 8b with that for $COCH_3$ as 0.502[10]).

Table III. Swain–Lupton Correlation Results for Substituted 1- Azulenecarboxylic Acids

Substituent position	f[a]	r[a]	i[a]	$\%\mathcal{R}$[a]	C[b]	n[c]
2[d]	1.23 ± 0.02	1.61 ± 0.04	−0.01	45.0 ± 0.04	0.9997	5
3	1.01 ± 0.09	0.97 ± 0.16	0.04	37 ± 4	0.992	7
6[d]	0.71 ± 0.06	0.93 ± 0.10	0.02	45 ± 3	0.997	4

[a] Parameters calculated as per ref 10. [b] Correlation coefficient. [c] Number of points in data set; each uses X = H. [d] Data set does not include strong electron-withdrawing groups.

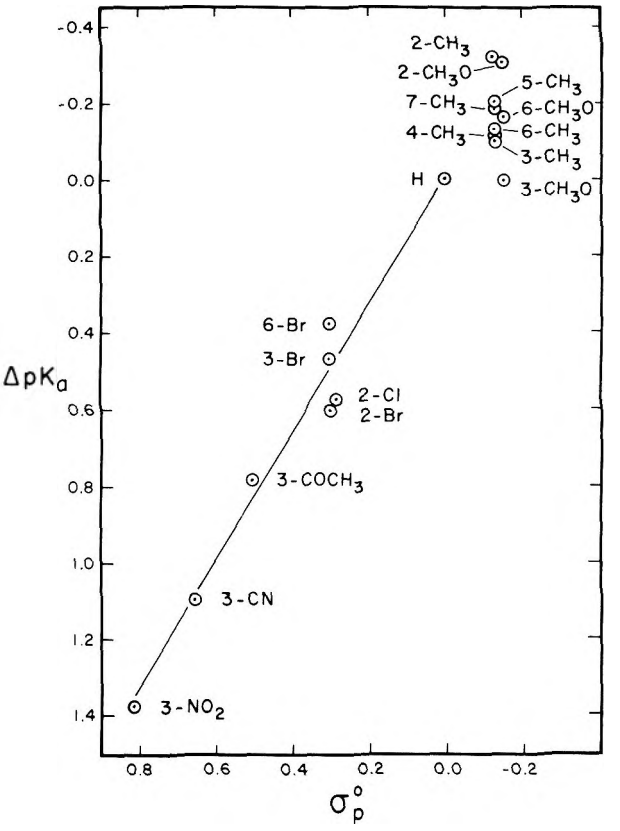


Figure 1. Plot of ΔpK_a's of X-1's against σ_p^0 constants. The line is that defined by electron-withdrawing 3-X-1's and 1.

Although the data sets of 2-X-1 and 6-X-1 are very limited we have applied the Swain–Lupton correlation[10] to

Table IV. Comparison of pK_a's of 2-X-1 and o-$XC_6H_4CO_2H$

	2-X-1		o-$XC_6H_4CO_2H$[17]	
H	pK_a[a]	ΔpK_a[c]	pK_a	ΔpK_a[c]
H	6.99		5.76[a,d] (4.20)[b]	
CH_3O	7.30	−0.31	5.83 (4.09)	−0.07[a,d] (0.11)[b]
CH_3	7.31	−0.32	5.78 (3.91)	−0.02 (0.29)
Cl	6.42	0.57	4.82 (2.94)	0.94 (1.26)
Br	6.39	0.60	4.73 (2.85)	1.03 (1.35)

[a] In 50% (v/v) aqueous ethanol at 25.0 °C. [b] In water at 25.00 °C.[17b] [c] pK_a (H) − pK_a (X). [d] Reference 17a.

them in an attempt to assess the sensitivities of these substituents to field and resonance effects. The resultant values are listed in Table III along with those of 3-X-1.

Comparing the empirical weighting factors *f* and *r* found for substituents at the 3 and 6 positions (Table III) we see that while these sensitivities to the resonance effect are the same, the sensitivity to the field effect is less at the 6 position. The latter was expected since the distance in azulene from the proton at C_1H to C_6 is 5.2 Å while the same distance (C_1H) to C_3 is 3.3 Å. This coupled with a poorer angle for charge–dipole interaction from C_6X to C_1H compared to C_3X (cos θ in the Kirkwood–Westheimer treatment of field effects)[15] leads to a reduced field effect by the 6 substituents.

The substituent effects by the 2 substituents in the pK_a's of 2-X-1 are interesting since they bear on the question of the ortho or proximity effect in ortho-substituted benzoic acid ionizations.[16] Table IV list the pK_a's of 2-X-1's and the corresponding o-$XC_6H_4CO_2H$'s[17] for comparison. We see that the change from water to 50% (v/v) aqueous ethanol has a parallel effect on the o-$XC_6H_4CO_2H$ ΔpK_a's. This was also observed by McCoy and Riecke[18] in the pK_a's of various o-alkylbenzoic acids in aqueous methanol.

As we change from o-$XC_6H_4CO_2H$ to 2-X-1 the distance between the X and CO_2H group increases owing to the geometric change involving a six-membered ring in o-$XC_6H_4CO_2H$ and a five-membered ring in 2-X-1. This change in geometry gave the large K_1/K_2 ratio of $10^{7.1}$ for 1,2-azulenedicarboxylic acid compared to 288 for this same ratio for phthalic acid.[3] In the cases of the CH_3O and CH_3 substituents especially, we find the *normal* effects of these substituents in 2-X-1 to be *acid weakening* which are almost negligible in the o-$XC_6H_4CO_2H$ series. Also, the substituent effects of o-Cl and o-Br on the pK_a of benzoic acid are larger in magnitude (greater acid-strengthening effect) than those found in 2-X-1's with X = Cl and Br. These latter differences are greater than those expected from the geometry changes in going from the six-membered ring of o-$XC_6H_4CO_2H$ to the five-membered ring of 2-X-1 using the field effect model with the same effective dielectric constant.[15]

We interpret this comparison as adequate evidence for a substantial contribution by *steric inhibition of resonance* to the overall effects in the ionization of o-$XC_6H_4CO_2H$'s realizing that factors such as steric inhibition of solvation and field and resonance effects are also operating.[18] The above data taken together with other recent reports[18,19] should satisfy even the most ardent critics of the presence of a significant contribution of steric inhibition of resonance in reactions of ortho-substituted benzoic acids.

The effect of the methyl group on the pK_a of 1 was determined at six of the seven nonequivalent ring positions (Table I and Figure 1). Omitting the 2-methyl effect due to the additional factors involved in the ortho effect, the remaining five methyl effects appear as roughly two groups

Table V. The CNDO/2 Regional Charges, q_r's, and Changes in Regional Charges, Δq_r's, Compared to Azulene for *syn*-1 and 1-Azulenecarboxylate Anion[20]

Ring position	q_r azulene	q_r *syn*-1	Δq_r[a] (*syn*-1)	q_r^- 1-$AzCO_2^-$	Δq_r^-[b] (1-$AzCO_2^-$)
3	5.084	5.081	0.00	5.119	−0.04
4	4.943	4.943	0.00	4.979	−0.04
5	5.025	5.007	+0.02	5.078	−0.05
6	4.942	4.940	0.00	4.978	−0.04
7	5.025	5.001	+0.02	5.069	−0.04

[a] $\Delta q_r = q_r$ (AzH) − q_r (*syn*-1). [b] $\Delta q_r^- = q_r$ (AzH) − q_r (1-Az-CO_2^-).

with the 3-, 4-, and 6-CH_3 effects being smaller than those found for the 5- and 7-CH_3 effects. In an attempt to understand these methyl substituent effects, we have modeled the reaction with CNDO/2 MO calculations[20] (*not structure minimized*) for the structures of 1 and its conjugate base. Calculations on *syn*- and *anti*-1 gave no significant changes in the ring position regional charges, q_r's,[21] except for the 2 position, where a small change (0.01) was noted. The geometry of the azulene ring selected was that used in ab initio calculations[22] taken from x-ray crystallographic studies.[23] The other bond lengths and angles[24] were as follows: C_1–$C(O_2H)$, 1.48 Å; C=O, 1.24 Å; C(=O)–OH, 1.29 Å; C_1–C=O ∠, 122°; C_1–C(=O)–OH ∠, 118°; C–O in CO_2^-, 1.26 Å; O–C–O ∠ in CO_2^-, 126°. The q_r's and Δq_r's (compared to azulene, AzH) are listed in Table V for the five nonequivalent ring positions under consideration.

As expected, the carbonyl-ring interaction had only a small perturbing influence on the 3–7 ring positions; the predominant factor in the acid weakening of 1-azulenecarboxylic acid (pK_a 6.99) compared to benzoic acid (pK_a 5.80 in 50% H_2O–EtOH) was the large surplus of electron density at C_1 of the unsubstituted azulene system (AzH). What we do see in the Δq_r's in Table V is that electron density is lost from the 5 and 7 positions (also at the 2, 9, and 10 positions Δq_r's ~0.02, not shown in Table V) when we replace C_1H in AzH by C_1CO_2H. Since all of the Δq_r^-'s are more approximately equal, the major acid-weakening effects on the pK_a of 1 by the methyl substituent would be expected at the C_5 and C_7 ring positions, in agreement with the experimental results.[25]

We see that in the azulene nonequivalent ring positions relative to the $-CO_2H \rightleftarrows -CO_2^-$ reaction center at C_1, no truly meta position is found. While the methyl group effects at C_2–C_7 on the pK_a of 1 do show an alternating effect they center around σ_p^0 behavior. Qualitatively, we believe that this is the result of more efficient charge delocalization in the 1-azulyl group with a greater number of ring sites sharing the formal charge compared to that found in the isomeric, benzenoid 1- and 2-naphthoic acids.[26]

An interesting feature of our results to date is the variable nature of the substituent effects at C_3 in reactions of the 1-azulyl group. As we have pointed out in the present study, under the modest perturbing influence of 1 ionization the C_3 substituent effects are intermediate between meta- and paralike behavior. However, in k_Δ acetolysis of 3-substituted 2-(1-azulyl)ethyl tosylates[27] excellent correlation of the data (3-OCH_3 to 3-NO_2) with σ_p^0 constants is observed. While this is not expected when one considers only canonical resonance structures, it is predicted from molecular orbital approaches.

Experimental Section[28]

1-Trifluoroacetyl-2-methoxyazulene. To a solution of 130 mg (0.823 mmol) of 2-methoxyazulene[1a,30] in 20 ml of CCl_4 at room temperature was added 1 ml of $(CF_3CO)_2O$. The color changed

from blue to light red. After 5 min 100 ml of ether was added, and the organic solution was washed with five 50-ml portions of water, dried ($MgSO_4$), and evaporated. The residue was chromatographed on alumina[29] and an orange band was eluted with 1:1 benzene–CH_2Cl_2. The resulting orange solid was recrystallized from CH_2Cl_2–hexane to give 175 mg (83%) of the product as light orange needles: mp 100–101 °C; NMR (CCl_4, internal Me_4Si): τ 0.45 (m, C_8H, 1), 1.7–2.65 (m, $C_{4,5,6,7}H$'s, 4), 3.38 (s, C_3H, 1), and 5.85 (s, OCH_3, 3)

Anal. Calcd for $C_{13}H_9F_3O_2$: C, 61.42; H, 3.56. Found: C, 61.50; H, 3.91.

2-Methoxy-1-azuloic Acid (2-CH_3O-1). A mixture of 40 mg (0.16 mmol) of 1-trifluoroacetyl-2-methoxyazulene and 400 mg of KOH in 5 ml of 50% aqueous ethanol was heated under reflux for 4 h. This solution was poured into water and extracted with CH_2Cl_2. The aqueous layer was acidified with dilute hydrochloric acid and the acid was extracted with CH_2Cl_2 which was dried (Na_2SO_4) and evaporated. The crude orange acid was recrystallized from $CHCl_3$–hexane giving 27 mg (85%) of orange crystals, mp 174–175 °C.

Anal. Calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.98. Found: C, 71.02; H, 5.00.

1-Trifluoroacetyl-2-methylazulene. 2-Methylazulene[1a,30] (110 mg, 0.78 mmol) was trifluoroacetylated as above. After work-up, the residue was chromatographed on alumina[29] where 1:1 benzene–CH_2Cl_2 eluted a red band leaving a large diffuse red band near the top of the column. The eluted band was evaporated and the solid recrystallized from hexane at −20 °C to give 60 mg (33%) of the desired product as red needles: mp 49–50 °C; NMR (CCl_4, internal Me_4Si) τ 0.70 (m, C_8H, 1), 1.5–2.8 (m, $C_{4,5,6,7}H$'s, 4), 2.90 (s, C_3H, 1), and 5.20 (s, CH_3, 3).

Anal. Calcd for $C_{13}H_9F_3O$: C, 65.55; H, 3.81. Found: C, 65.80; H, 3.56.

The apparent reason for the low yield of the product was hydrolysis on the alumina column.

2-Methyl-1-azuloic Acid (2-CH_3-1). Base hydrolysis of 60 mg (0.25 mmol) of 1-trifluoroacetyl-2-methylazulene as above and work-up afforded 25 mg (53%) of maroon crystals (recrystallized from ether–hexane), mp 180–190 °C dec.

Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.50; H, 5.27.

1-Trifluoroacetyl-2-chloroazulene. The trifluoroacetylation of 780 mg (4.8 mmol) of 2-chloroazulene[30] was carried out as above. The product was chromatographed on deactivated (3% water) alumina.[29] CH_2Cl_2 developed a single, broad, violet band that was eluted with $CHCl_3$ to afford 1.240 g (100%) of the title compound. Crystallization from ethanol afforded large, red plates: mp 88.0–88.5 °C; ir (KBr) 6.12 μ (s, C=O); NMR ($CDCl_3$, internal Me_4Si) τ 0.43–0.77 (m, C_8H, 1), 1.50–1.85 (m, C_4H, 1), 1.87–2.67 (m, $C_{5,6,7}H$'s, 3), and 2.77 (s, C_3H, 1); λ_{max} (CH_2Cl_2) 275 nm (log ϵ 4.44), 323 (4.61), 376 (4.15) (sh), 392 (4.13) (sh), and 495 (2.95).

Anal. Calcd for $C_{12}H_6F_3ClO$: C, 55.72; H, 2.34. Found: C, 55.55; H, 2.46.

Methyl 2-Chloro-1-azulenecarboxylate. 1-Trifluoroacetyl-2-chloroazulene (1.90 g, 7.34 mmol) was base hydrolyzed as above to give 1.44 g (95%) of crude 2-chloroazuloic acid (2-Cl-1). To 1.590 g (7.7 mmol) of crude 2-Cl-1 in 500 ml of ethyl acetate was added an excess of an ethereal CH_2N_2 solution. This mixture was allowed to stand for 30 min, the solvent volume reduced, and the residue chromatographed on alumina.[29] Benzene eluted a narrow, yellow band that was not investigated, and a broad, red band that afforded 1.470 g (87%) of the title compound. CH_2Cl_2 eluted a narrow, yellow-orange band that was not investigated. Crystallization from ethanol afforded fine, red needles of the ester: mp 86.0–86.5 °C; ir (KBr) 5.92 (s, C=O) and 9.55 μ (s, C–O); NMR ($CDCl_3$, internal Me_4Si) τ 0.38–0.72 (m, C_8H, 1), 1.57–1.87 (m, C_4H, 1), 2.05–2.67 (m, $C_{5,6,7}H$'s, 3), 2.78 (s, C_3H, 1), and 6.02 (s, CO_2CH_3, 3); λ_{max} (CH_2Cl_2) 294 nm (log ϵ 4.72), 304 (4.77), 340 (3.81), 350 (3.84), 366 (3.51), 515 (2.72), 538 (2.70) (sh), and 590 (2.28) (sh).

Anal. Calcd for $C_{12}H_9O_2Cl$: C, 65.32; H, 4.11. Found: C, 65.62; H, 3.97.

2-Chloro-1-azuloic Acid (2-Cl-1). Methyl 2-chloro-1-azulenecarboxylate (130 mg, 0.58 mmol) was hydrolyzed with 400 mg of KOH in 8 ml of 80% aqueous ethanol heated under reflux for 30 min. Work-up gave 80 mg (39%) of 2-Cl-1 as maroon crystals which were recrystallized from $CHCl_3$–hexane as maroon needles, mp 235–237 °C dec (ready sublimation >170 °C).

Anal. Calcd for $C_{11}H_7O_2Cl$: C, 63.94; H, 3.41. Found: C, 63.61; H, 3.51.

1-Trifluoroacetyl-2-bromoazulene. 2-Bromoazulene[1a] (90 mg, 0.44 mmol) was trifluoroacetylated as above. After work-up, the residue was chromatographed on alumina.[29] Benzene eluted a violet band, that yielded 30 mg of unreacted 2-bromoazulene, and a red band that was not investigated. $CHCl_3$ developed a violet band that eluted as a red-colored solution, affording 50 mg (38%, 57% net) of the title compound that slowly crystallized upon standing: mp 77.0–78.0 °C; ir (KBr) 6.06 μ (s, C=O); NMR ($CDCl_3$, internal Me_4Si) τ 0.92 [d (J = 10 Hz), C_8H, 1], 1.63 [d (J = 10 Hz), C_4H, 1], 2.00–2.57 (m, $C_{5,6,7}H$'s, 3), and 2.65 (s, C_3H, 1); λ_{max} (cyclohexane) 270 nm (log ϵ 4.28), 276 (4.34), 315 (4.56), 325 (4.59), 352 (3.87), 513 (2.80), 540 (2.77), and 590 (2.35).

Anal. Calcd for $C_{12}H_6F_3BrO$: C, 47.55; H, 2.00. Found: C, 47.80; H, 2.23.

2-Bromo-1-azuloic Acid (2-Br-1). 1-Trifluoroacetyl-2-bromoazulene (40 mg, 0.13 mmol) was hydrolyzed with base as above. Work-up gave 20 mg (61%) of maroon crystals of 2-Br-1, mp 226–228 °C dec (ready sublimation >180 °C).

Anal. Calcd for $C_{11}H_7O_2Br$: C, 52.61; H, 2.81. Found: C, 52.51; H, 2.50.

1-Trifluoroacetyl-2-iodoazulene. 2-Iodoazulene[30] (280 mg, 1.11 mmol) was trifluoroacetylated as above. After work-up, the residue was chromatographed on alumina[29] where hexane eluted a violet band containing 50 mg of 2-iodoazulene. CH_2Cl_2 developed a violet-blue band that was eluted with ethanol which afforded 295 mg (76%, 93% net) of the title compound. Crystallization from hexane afforded red needles: mp 90.0–90.5 °C; ir (KBr) 6.05 μ (s, C=O); NMR (CCl_4, internal Me_4Si) τ 0.98–1.60 (m, C_8H, 1), 1.53–1.90 (m, C_4H, 1), and 1.93–2.75 (m, 4); λ_{max} (cyclohexane) 274 nm (log ϵ 4.23), 323 (4.50), 334 (4.50), 362 (3.93) (sh), 523 (2.78), and 552 (2.75) (sh).

Anal. Calcd for $C_{12}H_6F_3IO$: C, 41.17; H, 1.73. Found: C, 41.21; H, 1.79.

2-Iodo-1-azuloic Acid (2-I-1). 1-Trifluoroacetyl-2-iodoazulene (270 mg, 0.77 mmol) was hydrolyzed with base as above. After work-up, the combined ethereal extracts gave 230 mg (100%) of 2-I-1. Recrystallization from $CHCl_3$ afforded silky, violet needles: mp 210–212 °C dec; ir (KBr) 6.08 (s, C=O) and 8.10 μ (s); NMR (Me_2SO-d_6, internal Me_4Si)[33] τ 0.00–0.67 (m, C_8H, 1), 1.50–1.62 (m, C_4H, 1), and 1.75–2.62 (m, 4); λ_{max} (CH_2Cl_2) 295 nm (log ϵ 4.64), 306 (4.74), 316 (4.43) (sh), 350 (3.84) (sh), 364 (3.72) (sh), and 515 (2.83).

Anal. Calcd for $C_{11}H_7O_2I$: C, 44.32; H, 2.37. Found: C, 44.43; H, 2.58.

Methyl 2-Iodo-1-azulenecarboxylate (2). 2-Iodo-1-azuloic acid (100 mg, 0.34 mmol) in 100 ml of ether was treated with an excess of ethereal CH_2N_2. After standing for 10 min, the solvent volume was reduced and the residue was chromatographed on alumina[29] where CH_2Cl_2 eluted a single, lavender band that afforded 104 mg (98%) of the title compound. Crystallization from CCl_4 yielded lavender needles: mp 65.0–66.5 °C; ir (neat film) 5.88 (s, C=O) and 9.55 μ (s, C–O); NMR (CCl_4, internal Me_4Si) τ 0.28–0.58 (m, C_8H, 1), 1.63–1.92 (m, C_4H, 1), 2.03–2.90 (m, 4), and 6.07 (s, CO_2CH_3, 3); λ_{max} (cyclohexane) 304 nm (log ϵ 4.71), 317 (4.73), 346 (4.08), 363 (4.12), 532 (2.71), 565 (2.68), and 615 (2.30) (sh).

Anal. Calcd for $C_{12}H_9O_2I$: C, 46.18; H, 2.91. Found: C, 46.23; H, 2.98.

Methyl 2-Cyano-1-azulenecarboxylate. To 155 mg (0.495 mmol) of **2** in 10 ml of dry (distilled from BaO) DMF was added 67 mg (0.75 mmol) of CuCN. The mixture was heated at 140–150 °C for 3.5 h as the color gradually changed from red to blue. This mixture was cooled, diluted with 100 ml of benzene, and washed with six 100-ml portions of warm aqueous NaCN (prepared from 20 g of NaCN and 600 ml of warm water). The blue, benzene layer was washed with 100 ml of water and dried (Na_2SO_4), the solvent volume reduced, and the residue chromatographed on alumina.[29] Benzene-CH_2Cl_2 (1:1) eluted a narrow, violet band that afforded 20 mg of unreacted **2**. Continued elution afforded a broad, blue band that yielded 82 mg (78%, 90% net) of the title compound. Crystallization afforded lavender needles: mp 172–174 °C; ir (KBr) 4.52 (m, C≡N), 5.92 (s, C=O), and 9.50 μ (s, C–O); NMR ($CDCl_3$, internal Me_4Si) τ 0.12–0.38 (m, C_8H, 1), 1.32–1.58 (m, C_4H, 1), 1.83–2.67 (m, 4), and 5.98 (s, CO_2CH_3, 3); λ_{max} (95% ethanol) 261 nm (log ϵ 4.18), 295 (4.72), 306 (4.82), 347 (4.03), 361 (3.75), 545 (2.96) (sh), and 568 (2.99).

Anal. Calcd for $C_{13}H_9O_2N$: C, 72.93; H, 4.29; N, 6.63. Found: C, 74.09; H, 4.22; N, 6.44.

2-Cyano-1-azuloic Acid (2-CN-1). To 83 mg (0.394 mmol) of methyl 2-cyano-1-azulenecarboxylate in 8 ml of ethanol was added 150 mg (2.68 mmol) of KOH in 2 ml of water. This mixture was heated under reflux for 15 min, diluted with 100 ml of water, and

extracted with 50 ml of ether to remove unreacted material. The aqueous portion was acidified with 10% hydrochloric acid and extracted with five 200-ml portions of ether. The combined ethereal extracts were washed with 500 ml of water and dried (Na_2SO_4), and the solvent volume reduced to yield 73 mg (95%) of the title compound. Crystallization from ethanol yielded violet needles: mp 293–294 °C; ir (KBr) 4.52 (m, C≡N) and 6.05 μ (s, C=O); NMR (Me_2SO-d_6, internal Me_4Si) τ −3.05 (broad s, CO_2H, 1), 0.12–0.42 (m, C_8H, 1), 1.00–1.37 (m, C_4H, 1), and 1.50–2.67 (m, 4); λ_{max} (95% ethanol) 261 nm (log ε 4.04), 294 (4.52), 306 (4.59), 347 (3.88), 360 (3.58), 545 (2.89) (sh), and 568 (2.90).

Anal. Calcd for $C_{12}H_7O_2N$: C, 73.09; H, 3.58. Found: C, 72.88; H, 3.81.

1-Trifluoroacetyl-3-methoxyazulene. 1-Methoxyazulene[1a] (75 mg, 0.50 mmol) was trifluoroacetylated as above. After work-up, the residue was chromatographed on alumina.[29] Benzene eluted a green band that yielded 125 mg (100%) of the title compound. Crystallization from hexane afforded long, dark-green needles: mp 92.0–92.5 °C; ir (KBr) 6.09 (s, C=O) and 9.44 μ (s, C–O); NMR (CCl_4, internal Me_4Si) τ 0.18–0.53 (m, C_8H, 1), 1.43–1.73 (m, C_4H, 1), 2.17–2.87 (m, 4), and 5.97 (s, OCH_3, 3); λ_{max} (cyclohexane) 282 nm (log ε 4.19), 313 (4.30), 319 (4.32), 327 (4.43), 423 (3.99), 450 (4.04), 576 (2.67), 610 (2.72), 623 (2.73), 657 (2.62), 682 (2.56), 735 (2.16), and 765 (2.00).

Anal. Calcd for $C_{13}H_9F_3O_2$: C, 61.42; H, 3.57. Found: C, 61.35; H, 3.47.

3-Methoxy-1-azuloic Acid (3-CH_3O-1). To a cool (ice bath) solution of 130 mg (0.82 mmol) of 1-methoxyazulene[1a] in 5 ml of dry benzene was added 1.0 ml of a 12.5% solution of $COCl_2$ in benzene for 5 min. This mixture was allowed to warm to room temperature and after 45 min 5 ml of water was added. Following 10 min of additional stirring, the mixture was diluted with 50 ml of water and 50 ml of ether. The layers were separated and the extraction repeated with two 50-ml portions of ether. The combined ethereal extracts were extracted with three 50-ml portions of 10% aqueous KOH, the ethereal layer discarded, and the aqueous portion washed with four 50-ml portions of $CHCl_3$ which removed a brown coloration. The blue-green aqueous portion was acidified with 10% hydrochloric acid and extracted with three 100-ml portions of ether. These combined ethereal extracts were washed with 150 ml of water and dried (Na_2SO_4), the solvent volume reduced, and the green residue chromatographed on silica gel with 3:1 CH_2Cl_2–ether. A narrow, green band eluted followed closely by a broad, blue band. The green band was not investigated and the broad, blue band afforded 48 mg (29%) of the title compound. Crystallization from 3:1 $CHCl_3$–hexane gave green needles: mp 201–202 °C; ir (KBr) 6.04 μ (s, C=O); NMR ($CDCl_3$, internal Me_4Si)[33] τ 0.35–0.65 (m, C_8H, 1), 1.42–1.68 (m, C_4H, 1), 2.15 (s, C_2H, 1), 2.23–3.00 (m, $C_{5,6,7}H$'s, 3), and 5.93 (s, OCH_3, 3); λ_{max} (CH_2Cl_2) 301 nm (log ε 4.46), 308 (4.46), 313 (4.53), 405 (3.89) (sh), and 620 (2.68).

Anal. Calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.99. Found: C, 71.14; H, 5.03.

Methyl 3-Methoxy-1-azulenecarboxylate. 3-CH_3O-1 (118 mg, 0.58 mmol) was esterified with CH_2N_2 as above. After work-up, the residue was chromatographed on alumina.[29] CH_2Cl_2 eluted a small, green band that was not investigated and a broad, blue band that afforded 75 mg (60%) of the title compound, as a green oil which crystallized from 1:1 hexane–CCl_4 to yield green rosettes: mp 62.0–62.5 °C; ir (neat film) 5.98 (s, C=O) and 9.79 μ (s, C–O); NMR (CCl_4, internal Me_4Si) τ 0.42–0.72 (m, C_8H, 1), 1.45–1.75 (m, C_4H, 1), 2.20–3.10 (m, $C_{2,5,6,7}H$'s, 4), 6.00 (s, OCH_3, 3), and 6.13 (s, CO_2CH_3, 3); λ_{max} (cyclohexane) 287 nm (log ε 4.39), 291 (4.50), 298 (4.61), 305 (4.57), 311 (4.67), 382 (3.96), 409 (4.07), 623 (2.59), 640 (2.62), 675 (2.54), 706 (2.54), and 755 (2.14).

Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.60. Found: C, 71.96; H, 5.40.

1-Trifluoroacetyl-3-methylazulene. 1-Methylazulene[1a,4] was trifluoroacetylated as above. After work-up, the residue was chromatographed on alumina.[29] Benzene eluted a narrow green band that was not investigated, followed by a broad, brown-red band that afforded 278 mg (66%) of the title compound. Crystallization from hexane yielded long, brown plates: mp 96.0–96.5 °C; ir (KBr) 6.10 μ (s, C=O); NMR (CCl_4, internal Me_4Si) τ 0.17–0.50 (m, C_8H, 1), 1.59–1.80 (m, C_4H, 1), 1.83–2.75 (m, 4), and 7.42 (s, CH_3, 3); λ_{max} (cyclohexane) 272 nm (log ε 4.20), 298 (4.37), 309 (4.45), 316 (4.54), 392 (4.05), 415 (4.11), 553 (2.74), 596 (2.62), 632 (2.20), and 658 (2.11).

Anal. Calcd for $C_{13}H_9F_3O$: C, 65.54; H, 3.80. Found: C, 65.45; H, 3.70.

3-Methyl-1-azuloic Acid (3-CH_3-1). 1-Trifluoroacetyl-3-methylazulene (278 mg, 1.17 mmol) was hydrolyzed with base as above. After work-up, the solid residue was washed with five 10-ml portions of hexane which removed a yellow substance (not investigated). The remaining residue afforded 132 mg (60%) of the title compound. Crystallization from ether yielded long, fine, gray needles: mp 195–196 °C; ir (KBr) 6.10 (s), 7.00 (s), and 9.09 μ (s); NMR (Me_2SO-d_6, internal Me_4Si) τ −2.22 (broad s, CO_2H, 1), 0.32–0.62 (m, C_8H, 1), 1.32–1.65 (m, C_4H, 1), 1.82 (s, C_2H, 1), 2.00–2.72 (m, $C_{5,6,7}H$'s, 3), and 7.38 (s, CH_3, 3); λ_{max} (95% ethanol) 291 nm (log ε 4.64), 296 (4.63), 303 (4.72), 366 (3.91), 380 (3.99), 564 (2.63), and 665 (2.40) (sh).

Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.70; H, 5.67.

Methyl 3-Bromo-1-azulenecarboxylate. A mixture of 230 mg (0.12 mmol) of methyl 1-azulenecarboxylate[4] and 0.40 g of *N*-bromosuccinimide in 25 ml of benzene was stirred at room temperature for 20 min, then poured onto an alumina[29] column. A blue band eluted which solidified on solvent evaporation. Recrystallization from CH_2Cl_2–hexane at −30 °C gave 273 mg (83%) of the desired ester as blue crystals: mp 89–90 °C; NMR (CCl_4, internal Me_4Si) τ 0.42 (m, C_8H, 1), 1.4–2.8 (m, $C_{2,4,5,6,7}H$'s with C_2H as s at τ 1.73, 5), and 6.13 (s, CH_3, 3).

Anal. Calcd for $C_{12}H_9O_2Br$: C, 54.37; H, 3.42. Found: C, 54.10; H, 3.26.

Methyl 3-Acetyl-1-azulenecarboxylate. To a solution of 250 mg (1.34 mmol) of methyl 1-azulenecarboxylate[4] in 5 ml of acetic anhydride was added 0.3 ml of $SnCl_4$ in 50 ml of CH_2Cl_2. After work-up, the residue was chromatographed on alumina[29] where CH_2Cl eluted a deep-red band of the product. Recrystallization from CH_2Cl_2–hexane at −30 °C gave 180 mg (50%) of the desired ester: mp 120–121 °C; NMR (CCl_4, internal Me_4Si) τ −0.2 to 0.1 (m, $C_{4,8}H$'s, 2), 1.27 (s, C_2H, 1), 2.0–2.5 (m, $C_{5,6,7}H$'s, 3), 6.1 (s, CH_3, 3), and 7.39 (s, CH_3, 3).

Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.80; H, 5.47.

Methyl 3-Cyano-1-azulenecarboxylate. To a cool (ice bath) solution of 250 mg (1.34 mmol) of methyl 1-azulenecarboxylate[4] and 1.45 g (13.4 mmol) of BrCN in 25 ml of ether was added dropwise 1.55 ml of $SnCl_4$. After stirring overnight at room temperature and work-up, the residue was chromatographed on alumina.[29] Benzene eluted a blue band containing 94 mg (25%) of methyl 3-bromo-1-azulenecarboxylate identical with that prepared above. CH_2Cl_2 eluted a red band containing 95 mg (34%) of the desired cyano ester: mp 141–142 °C; NMR (CCl_4, internal Me_4Si) τ 0.1–2.5 (m, $C_{2,4,5,6,7,8}H$'s with C_2H as s at τ 1.5, 6) and 6.08 (s, CH_3, 3).

Anal. Calcd for $C_{13}H_9NO_2$: C, 73.92; H, 4.29. Found: C, 73.95; H, 4.37.

Methyl 3-Nitro-1-azulenecarboxylate. To a solution of 290 mg (1.56 mmol) of methyl 1-azulenecarboxylate[4] in 15 ml of acetic anhydride was added 600 mg of $Cu(NO_3)_2$ in 25 ml of acetic anhydride over a 10-min period. After 15 min of stirring and work-up, the residue was chromatographed on alumina[29] with benzene. Benzene eluted a yellow band which may have been 1,3-dinitroazulene. CH_2Cl_2 eluted a red band containing the nitro ester. Recrystallization afforded 90 mg (25%) of the product: mp 145–147 °C; NMR ($CDCl_3$, internal Me_4Si) τ 0.0–0.4 (m, $C_{4,8}H$'s, 2), 1.24 (s, C_2H, 1), 1.6–2.5 (m, $C_{5,6,7}H$'s, 3), and 6.06 (s, CH_3, 3).

Anal. Calcd for $C_{12}H_9NO_4$: C, 62.34; H, 3.92; N, 6.06. Found: C, 62.73; H, 3.92; N, 5.83.

3-Bromo-, 3-Acetyl-, 3-Cyano-, and 3-Nitro-1-azuloic Acids. Each of the above esters was hydrolyzed with KOH in 50% aqueous methanol at room temperature for 3 h, then heated under reflux for 30 min. Extraction with ether removed any starting ester. Acidification and extraction of the desired acid into ether gave these compounds which were recrystallized from ether–hexane. 3-Br-1, mp 270 °C dec. Anal. Calcd for $C_{11}H_7BrO_2$: C, 52.62; H, 2.81. Found: C, 52.25; H, 2.65. 3-CH_3CO-1, mp 220–235 °C dec. Anal. Calcd for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 73.80; H, 4.86. 3-CN-1, mp 265–270 °C (sublimed). Anal. Calcd for $C_{12}H_7NO_2$: C, 73.09; H, 3.58; N, 7.10. Found: C, 73.00; H, 3.74; N, 7.24. 3-NO_2-1, mp 260–270 °C (sublimed). Anal. Calcd for $C_{11}H_7NO_4$: C, 60.83; H, 3.25; H, 6.45. Found: C, 60.45; H, 3.02; N, 6.21.

1-Trifluoroacetyl-4-methylazulene. 4-Methylazulene[7] (164 mg, 1.15 mmol) was trifluoroacetylated as above. Work-up gave a crude product which exhibited only a single CH_3 resonance in the NMR spectrum. This was chromatographed on alumina[29] where 1:1 CH_2Cl_2–benzene eluted the major component identified as the 4-methyl isomer which was recrystallized from hexane: mp 73.0–73.5 °C; NMR (CCl_4, internal Me_4Si) τ 0.22–0.49 (m, C_8H, 1), 1.75–3.0 (m, $C_{2,3,5,6,7}H$'s, 5), and 7.15 (s, CH_3, 3).

Anal. Calcd for $C_{13}H_9F_3O$: C, 65.55; H, 3.81. Found: C, 65.60; H, 3.65.

4-Methyl-1-azuloic Acid (4-CH_3-1). 1-Trifluoroacetyl-4-methylazulene (60 mg, 0.25 mmol) was hydrolyzed with base as previously described. Work-up gave 40 mg of 4-CH_3-1 which was recrystallized from ether–hexane as purple crystals: mp 185–188 °C dec (lit.[31] mp 192–193 °C dec); NMR ($CDCl_3$, internal Me_4Si)[33] τ 0.15–0.30 (m, C_8H, 1), 1.55 (d, C_2H, 1), and 2.1–3.0 (m, $C_{3,5,6,7}H$'s, 4).

5- (5-CH_3-1) and 7-Methyl-1-azuloic Acids (7-CH_3-1). A mixture of methyl 5- and 7-methyl-1-azulenecarboxylates was available from the reaction series (1) formation of the Meisenheimer type complex by 6 addition of lithium dicyclohexylamide to 5-methylazulene, (2) carbonation, and (3) formation of the methyl esters of the carboxylic acids.[6] Chromatography of this mixture on Woelm neutral, activity 1 alumina effected separation into two distinct bands; band 1 was eluted with cyclohexane and band 2 was eluted with CH_2Cl_2.

Band 1 was identified as methyl 7-methyl-1-azulenecarboxylate (5) on the basis of its NMR spectrum (CCl_4, internal Me_4Si): τ 0.35 (broadened s with some coupling indicated, C_8H, 1), 1.60–3.0 ($C_{2,3,4,5,6}H$'s, 5), 6.15 (s, OCH_3, 3), and 7.21 (s, CH_3, 3).

Band 2 was identified as methyl 5-methyl-1-azulenecarboxylate (4) on the basis of its NMR spectrum (CCl_4, internal Me_4Si) τ 0.54 (d of d's, C_8H, 1), 1.60–3.0 ($C_{2,3,4,6,7}H$'s, 5), 6.17 (s, OCH_3, 3), and 7.25 (s, CH_3, 3).

Base hydrolysis of each of these esters in 50% aqueous methanol afforded their respective acids, 7-CH_3-1, mp 189–190 °C dec, and 5-CH_3-1, mp 192–193 °C dec, in >90% yield.

Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: (7-CH_3-1) C, 77.12; H, 5.40; (5-CH_3-1) C, 77.42; H, 5.52.

6-Methoxy-1-azuloic Acid (6-CH_3O-1). 6-Methoxyazulene[1a] (132 mg, 0.84 mmol) was allowed to react with $COCl_2$ in benzene for 1 h at 0 °C by the method used in preparing 3-CH_3O-1. After work-up, 60 mg (36%, 73% net) of 6-CH_3O-1 was obtained. Crystallization from ether afforded orange plates: mp 194.5–195.0 °C; ir (KBr) 6.15 μ (s, C=O); NMR (Me_2SO-d_6, internal Me_4Si)[33] τ 0.25–0.73 (m, C_8H, 1), 1.40–1.75 (m, C_4H, 1), 1.93 [d (J = 4 Hz), C_2H, 1], 2.43–3.07 (m, $C_{3,5,6,7}H$'s, 4), and 5.95 (s, OCH_3, 3); λ_{max} (95% ethanol) 302 nm (log ϵ 4.65) (sh), 314 (4.72), 346 (3.92), 357 (3.90), 370 (3.63) (sh), and 485 (2.72).

Anal. Calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.99. Found: C, 71.00; H, 5.10.

6-Methyl-1-azuloic Acid (6-CH_3-1). A sample (110 mg) of methyl 6-methyl-1-azulenecarboxylate was available from the study that produced the mixture of methyl 5- and 7-methyl-1-azulenecarboxylates.[6] This sample was chromatographed on deactivated (10% H_2O) silica gel with benzene. The solvent was evaporated from the eluate and the ester was hydrolyzed with KOH in 50% aqueous methanol. Work-up gave the acid which was chromatographed on deactivated (10% H_2O) silica gel with 1:1 CH_2Cl_2–ether. The acid was recrystallized from ether–hexane, giving 65 mg of 6-CH_3-1 as deep red crystals, mp 206–208 °C dec.

Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.31; H, 5.12.

Methyl 6-Bromo-1-azulenecarboxylate. 6-Bromoazulene[1a] (75 mg, 0.36 mmol) was allowed to react with $COCl_2$ in benzene at room temperature for 60 h as above. After work-up, 45 mg (50%, 100% net) of crude 6-Br-1 was obtained. This was dissolved in ether and treated with an excess of ethereal CH_2N_2. After work-up, the residue was chromatographed on alumina[29] with benzene. A violet band eluted, leaving behind a tightly held yellow band which was not investigated. The violet band afforded 115 mg (78%) of the title copound. Recrystallization from ether yielded flat, purple needles, with a sweet aroma: mp 101.2–102.0 °C; ir (KBr) 5.95 (s, C=O) and 9.60 μ (s, C–O); NMR ($CDCl_3$, internal Me_4Si) τ 0.48–0.88 (m, C_8H, 1), 1.57–2.58 (m, 4), 2.70 [d (J = 4 Hz), C_3H, 1], and 6.05 (s, CH_3, 3); λ_{max} (cyclohexane) 297 nm (log ϵ 4.81), 302 (4.28), 309 (4.89), 347 (3.79), 355 (3.88), 373 (3.85), 547 (2.58), 592 (2.50), and 650 (2.07).

Anal. Calcd for $C_{12}H_9O_2Br$: C, 54.36; H, 3.42. Found: 54.38; H, 3.47.

6-Bromo-1-azuloic Acid (6-Br-1). A 10-ml solution of DMF containing 3.0 g of lithium bromide hydrate and 2 g of crushed 2A molecular sieves under nitrogen was heated for 30 min under reflux and then 115 mg (0.435 mmol) of methyl 6-bromo-1-azulenecarboxylate in 5 ml of DMF was added dropwise. This solution was heated under reflux for 4 h, cooled, diluted with 200 ml of ether, and extracted with five 75-ml portions of 5% aqueous sodium bicarbonate. The combined aqueous layers were acidified with 10% hydrochloric acid and extracted with three 50-ml portions of ether. The combined ethereal layers were dried (Na_2SO_4) and the solvent volume reduced to yield 50 mg (46%) of 6-Br-1 which was recrystallized from THF, giving violet needles: mp 250–253 °C (sealed capillary); ir (KBr): 6.02 μ (s, C=O); NMR ($CDCl_3$, internal Me_4Si)[33] τ 0.17–0.47 (m, C_8H, 1), and 1.38–2.87 (m, 5); λ_{max} (95% ethanol) 295 nm (log ϵ 4.71), 306 (4.75), 345 (3.76), 354 (3.80), 371 (3.72), 543 (2.62), 590 (2.53) (sh), and 650 (2.00) (sh). The log ϵ values are calculated assuming 100% purity of the acid. Although several samples were prepared and submitted for elemental analysis, no satisfactory analysis was obtained. The reason for this is unknown.

The neutral ethereal portion of the reaction mixture was dried (Na_2SO_4), the solvent volume reduced, and the residue chromatographed on alumina.[29] Hexane–CH_2Cl_2 (1:1) eluted a blue band that yielded 35 mg (39%) of 6-bromoazulene. CH_2Cl_2 eluted a pink band that afforded 10 mg (9% recovery) of unreacted methyl 6-bromo-1-azulenecarboxylate.

Determination of Dissociation Constants. The method used for determination of the dissociation constants of X-1's has been reported.[3] The method used zone defined benzoic acid as our primary standard to set the pH scale. The dissociation constants of several acids in water were then determined to evaluate the accuracy and precision of the method; these results are listed in Table VI. A probable reason for the small discrepancy in the pK_1 of succinic acid and the literature value is that we used reagent grade succinic acid while Wilcox and Leung[32] used zone refined material.

Table VI. Thermodynamic pK_a's in Water at 25.00 ± 0.01 °C

Acid	This work	Lit.[32]
Benzoic	4.199	4.199 ± 0.004
Acetic	4.757 ± 0.002	4.757 ± 0.004
Pivalic	5.031 ± 0.003	5.032 ± 0.002
Succinic (pK_1)	4.189 ± 0.001	4.206 ± 0.003
Succinic (pK_2)	5.637 ± 0.002	5.639 ± 0.004

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Registry No.—2-I-1, 58313-12-5; 2-CN-1, 58313-13-6; 2, 58342-98-6; 4, 51381-35-2; 5, 51381-36-3; 1-trifluoroacetyl-2-chloroazulene, 54798-15-1; 2-chloroazulene, 36044-31-2; methyl-2-chloro-1-azulenecarboxylate, 54798-16-2; 1-trifluoroacetyl-2-bromoazulene, 58313-14-7; 2-bromoazulene, 58312-57-5; 1-trifluoroacetyl-2-iodoazulene, 58313-15-8; 2-iodoazulene, 36044-41-4; methyl 2-cyano-1-azulenecarboxylate, 38287-28-4; 1-trifluoroacetyl-3-methoxyazulene, 41867-34-9; 1-methoxyazulene, 30264-97-2; methyl 3-methoxy-1-azulenecarboxylate, 58313-16-9; 1-trifluoroacetyl-3-methylazulene, 58313-17-0; 1-methylazulene, 769-31-3; methyl 3-bromo-1-azulenecarboxylate, 42081-17-4; methyl 1-azulenecarboxylate, 14659-03-1; methyl 3-acetyl-1-azulenecarboxylate, 58313-18-1; methyl 3-cyano-1-azulenecarboxylate, 38287-27-3; methyl 3-nitro-1-azulenecarboxylate, 41867-40-7; 1-trifluoroacetyl-4-methylazulene, 58313-19-2; 4-methylazulene, 17647-77-7; 5-methylazulene, 1654-55-3; 6-methoxyazulene, 35046-03-8; methyl 6-methyl-1-azulenecarboxylate, 51381-40-9; methyl 6-bromo-1-azulenecarboxylate, 58313-20-5; 6-bromoazulene, 35046-05-0; 2-methoxyazulene, 36044-37-8; 1-trifluoroacetyl-2-methoxyazulene, 58313-21-6; trifluoroacetic anhydride, 407-25-0; 1-trifluoroacetyl-2-methylazulene, 58313-22-7; 2-methylazulene, 769-86-8.

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An Efficient Synthesis of 1-β-D-Arabinofuranosylcytosine

Edward J. Hessler

Chemical Process Research and Development, The Upjohn Company, Kalamazoo, Michigan 49001

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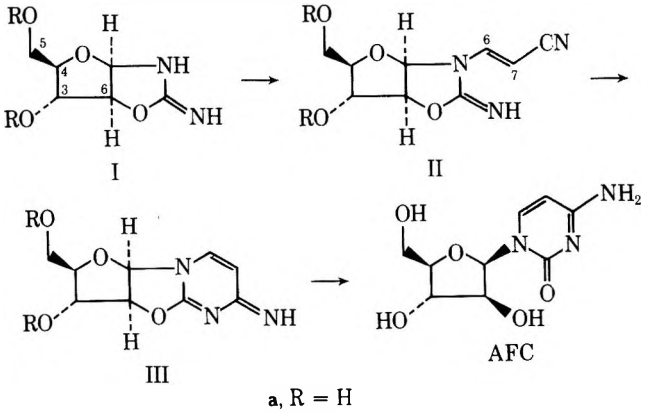
Isoxazole is treated with strong base at low temperature to form in high selectivity the cis enolate salt of cyanoacetaldehyde. Tosylation, followed by reaction with trimethylamine, furnishes *cis*-β-trimethylammoniumacrylonitrile tosylate in high yield. This product is treated with 2-amino-β-D-arabinofurano[1′,2′:4,5]-2-oxazoline to form the desired cis cyanovinyl adduct which is further converted to 1-β-D-arabinofuranosylcytosine.

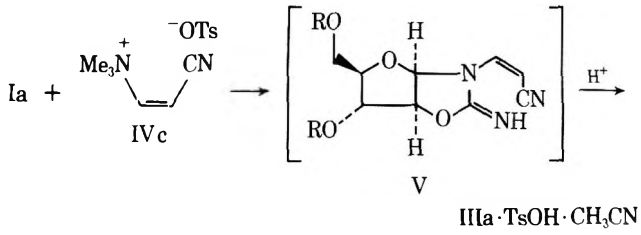
Cytosine arabinoside (1-β-D-arabinofuranosylcytosine, AFC) has been proven effective in the treatment of acute leukemias. Additionally, *anhydro*-AFC is being investigated as an antitumor agent. Since increasing amounts of AFC are being used medicinally a low-cost synthesis of AFC has been pursued in this and other laboratories. Very recently Sanchez and co-workers[1] published an elegant method to prepare AFC. The reaction of D-arabinose with cyanamide to form 2-amino-β-D-arabinofurano[1′,2′:4,5]-2-oxazoline (Ia) is followed by reaction of Ia with propiolonitrile to yield a cyanovinyl adduct which Sanchez formulates as the trans adduct IIa.



a, R = H
b, R = Me_3Si

Treatment of the cyanovinyl adduct with aqueous ammonia gave a high yield of AFC, presumably via 2,2′-anhydro-1-β-D-arabinofuranosylcytosine (IIIa). Our goal was to prepare AFC by a procedure that could ultimately be used in large-scale manufacture and by a procedure that allowed isolation of *anhydro*-AFC (III), if possible. Use of oxazoline I as an intermediate was favored since the oxazoline is of the correct configuration at C-1 of the arabinose moiety. Unfortunately the above process utilizes propiolonitrile, a compound that was judged too hazardous for large-scale synthesis. Our specific goal then became to find a substitute for the key reagent, propiolonitrile.

It was found that *cis*-β-trimethylammoniumacrylonitrile tosylate (IVc), a stable, white, crystalline solid, can be substituted for propiolonitrile in the synthesis. Reaction of IVc with oxazoline Ia was carried out best in DMF at 50 °C. Use of protic solvents such as water, methanol, or 2-propanol for the reaction gave only poor yields of AFC. However, dipolar aprotic solvents were effective, with DMF giving the highest yields. Addition of acetonitrile at the end of the reaction caused crystallization of a white solid isolated in 70–74% yield, which is assigned the acetonitrile solvate of 2,2′-*anhydro*-AFC tosylate salt (IIIa TsOH CH_3CN) by NMR comparison to authentic[1] 2,2′-*anhydro*-AFC hydrochloride. It is very likely that the *cis*-cyanovinyl adduct Va is generated as an intermediate which then cyclizes to IIIa in the presence of tosic acid.



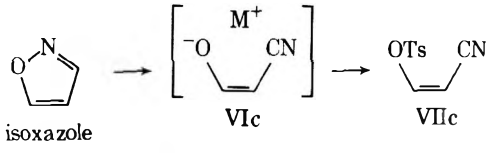
IIIa·TsOH·CH_3CN

AFC crystallizes very poorly in the presence of impurities. Since 2,2′-*anhydro*-AFC tosylate salt IIIa crystallizes so well, a great deal of purification is accomplished at this stage; additionally, the desired isolation of *anhydro*-AFC (III) is accomplished by crystallization.

Hydrolysis of IIIa TsOH CH_3CN to AFC occurs readily in dilute aqueous ammonia as reported earlier by Sanchez.[1] The product mixture consists of AFC, tosic acid, and a trace of a less polar component which has been tentatively assigned as 1-β-D-arabinofuranosyluracil by TLC comparison. Purification of AFC is achieved by adsorption, then elution from a sulfonic acid ion exchange resin.

Crystallization is accomplished from aqueous methanol to give AFC in 90% yield from IIIa. AFC prepared in this way was shown to be identical with authentic AFC by ir, uv, TLC, optical activity, and elemental analysis.

The key reagent for this synthesis is quaternary salt IVc. This compound is synthesized in high yield by reaction of isoxazole with base. According to the early literature,[2] isoxazole reacts with sodium methoxide–methanol to give an equilibrium mixture of enolate salts VIc + VIt (45:55) in quantitative yield. This equilibration must surely occur via protonation of cis enolate salt VIc to form cyanoacetaldehyde, followed by proton abstraction to give VIc + VIt in the equilibrium ratio. Cis enolate VIc is the sole product from reaction of isoxazole with potassium *tert*-butoxide–THF, if the reaction is carried out at −40 °C or lower. Temperature control of this step is crucial; if the temperature of the reaction is −28 °C, ca. 30% of the unwanted trans enolate salt VIt forms. Product VIc crystallizes out of the reaction mixture. Since it must be kept cold in order to avoid isomerization it is not isolated, but treated directly with tosyl chloride–acetonitrile. The enolate salt reacts upon dissolution to form *cis*-β-tosyloxyacrylonitrile (VIIc) before any significant isomerization occurs.



isoxazole VIc VIIc

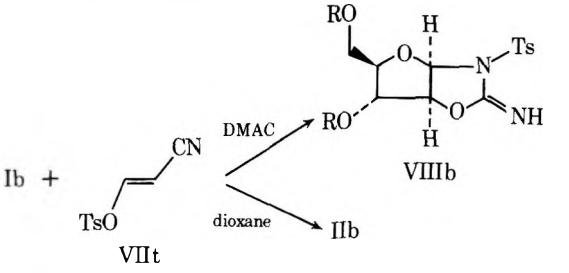
Compound VIIc is converted directly to quaternary salt IVc without isolation in the above reaction. The overall yield of IVc from isoxazole is 85–95%. The reaction with trimethylamine was expected on the basis of the reported[3] reaction of trimethylamine with β-chloroacrylonitrile.[4] It is a stereospecific addition–elimination process that occurs with retention, a result that parallels earlier published work[5] which described nucleophilic displacements of β-chlorocrotonate esters. Thus, cis tosylate VIIc yields only cis quaternary salt IVc (substantiated by NMR data; see Table I).

Other Approaches to AFC. In an earlier synthetic study the equilibrium mixture of enolate salts VIc + VIt was converted to the mixture of *cis*- and *trans*-β-tosyloxyacrylonitrile (VIIc + VIIt). These were separated and purified by silica gel chromatography.

The reaction of oxazoline I as its di-*O*-trimethylsilyl (Me_3Si) ether derivative (Ib) with VIIc and VIIt was examined. Curiously no reaction was observed with cis tosylate VIIc.[6] Reaction of oxazoline Ib with trans tosylate VIIt in the polar solvent *N*,*N*-dimethylacetamide (DMAC) produced, as the major product, a compound tentatively assigned the *N*-tosyloxazoline VIIIb. In nonpolar solvents such as dioxane a cyanovinyl adduct was produced, which was assigned the trans cyanovinyl adduct IIb.

Table I. Vinylic Coupling Constant Data

		τ H–C–CN	*J*, Hz
(II)	Tosylate cyanovinyl adduct	4.90	14.5
(V)	Propiolonitrile cyanovinyl adduct	5.43	10.5
(IVc)	Cis quaternary salt	3.45	10
(IVt)	Trans quaternary salt	3.23	14.5



VIIt

b, R = Me_3Si

Compound VIIIb, after silylation to the tri-Me_3Si derivative, showed intense *m/e* 529 and 480 peaks in its mass spectrum.[7] This is rationalized as follows: M^+ at *m/e* 544 not present; M − 15 (−Me) at *m/e* 529, and M − 64 ($-SO_2$) at *m/e* 480. The high-resolution mass spectral determination of the *m/e* 529 peak confirmed the elemental composition of VIIIb Me_3Si: calcd for *m/e* 529, 529.1680 ($C_{21}H_{37}O_8N_2SSi_3$), and found, 529.1673. We are not certain which nitrogen atom contains the tosyl group. Since the ring nitrogen atom is more nucleophilic, we assume that it is tosylated.

Compound IIb, designated the tosylate cyanovinyl adduct, after silylation to the tri-Me_3Si derivative, was analyzed by GLC and GLC–MS. A molecular ion of *m/e* 441 was observed. The high-resolution mass spectral determination of the *m/e* 441 peak confirmed the elemental composition for the cyanovinyl adduct (IIb Me_3Si): calcd for *m/e* 441, 441.1935 ($C_{18}H_{35}O_4N_3Si_3$) and found, 441.1927. It was assigned the trans stereochemistry by data presented below.

Because the tosylate cyanovinyl adduct had the correct molecular ion, we examined the known reaction[1] of propiolonitrile with oxazoline Ia in DMF, or with oxazoline Ib in Me_2SO, DMF, or $CHCl_3$. In all cases the reaction products were silylated and examined by GLC. Reaction in all the solvents gave a single product, designated as the propiolonitrile cyanovinyl adduct, which had a *different* retention time than that of the tosylate cyanovinyl adduct. However, the mass spectrum of the silylated propiolonitrile cyanovinyl adduct was identical with the mass spectrum of the silylated tosylate cyanovinyl adduct. Moreover, when the propiolonitrile cyanovinyl adduct from reaction of Ib in Me_2SO with propiolonitrile is treated with aqueous ammonia, conversion to AFC (by TLC) is rapid at room temperature, as already reported[1] for the nonsilylated cyanovinyl adduct. However, when the tosylate cyanovinyl adduct was treated with aqueous ammonia at room temperature, the only reaction that occurred is the hydrolysis of the silyl groups to give IIa. Uv and ir analysis of IIa indicated the presence of the cyanovinyl adduct unchanged; there was no AFC formed (by TLC). However, if the tosylate cyanovinyl adduct was stirred with aqueous ammonia at 90 °C, conversion to AFC did occur, presumably via thermal isomerization to the cis adduct Va, and then cyclization and hydrolysis to AFC. Presence of AFC

in the product was proven by preparative TLC, uv, and GLC/MS analysis.

NMR analysis of the tosylate cyanovinyl adduct and the propiolonitrile cyanovinyl adduct showed the vinylic proton coupling constants in Table I. The NMR analysis shows that the larger coupling constant, normally assigned to trans isomers, occurs for the tosylate cyanovinyl adduct.

The Sanchez group has suggested in their latest publication[1] that the propiolonitrile cyanovinyl adduct is a trans cyanovinyl adduct (as in II). Our data (NMR analysis and reactivity of the two isomers) require that the cyanovinyl adduct from propiolonitrile is cis (as in V) and the cyanovinyl adduct from *trans*-β-tosyloxyacrylonitrile is trans (as in II).[8]

Although the trans cyanovinyl adduct II can be converted to AFC by photoisomerization in aqueous ammonia, or by thermal isomerization, we discarded this approach because isolation of β-*trans*-tosyloxyacryonitrile is very cumbersome. Investigation of the reactions of the *cis*- and *trans*-β-trimethylammoniumacrylonitrile tosylates then led to the final procedure.

Experimental Section[9]

After study of the reported[1] procedure to prepare oxazoline Ia, the reaction conditions were modified considerably. Reaction of D-arabinose with cyanamide is best carried out in DMF. Potassium bicarbonate is required in catalytic quantities.

2-Amino-β-D-arabinofurano[1′,2′4,5]-2-oxazoline (Ia). A mixture of 90.0 g (600 mmol) of D-arabinose, cyanamide (31.0 g, 740 mmol, 1.23 equiv), and mortared potassium bicarbonate (3.60 g, 36 mmol, 0.06 equiv) was stirred at 90 °C in 600 ml of DMF. After ca. 5 min, the mixture was a pale yellow solution, and after another 6 min, the solution deposited crystals of product. It was stirred for 75 min at 90 °C after the product precipitated, then was cooled to 30 °C. Ethyl acetate (360 ml) was added over ~15 min, and the suspension was stirred for 30 min at 25 °C and 1 h at 0 °C. The crystals were filtered, washed with 2 × 100 ml of 1:1 ethyl acetate–DMF and then 150 ml of ethyl acetate, and dried at 60 °C under house vacuum (27 in. Hg) overnight to give 88.1 g (85%) of off-white crystalline oxazoline II, mp 173.5–174.5 °C. This material is suitable for the next step, although purest quality oxazoline is a white solid of mp 181–183 °C.

2-Amino-β-D-arabinofuran[1′,2′:4,5]-2-oxazoline Di-*O*-trimethylsilyl Ether (Ib). D-Arabinose (30.0 g, 0.20 mol), cyanamide (8.6 g, 0.205 mol), 200 ml of DMF, and 2.0 g of mortared potassium bicarbonate were stirred at 90 °C for 50 min. The mixture was cooled to room temperature, 0.60 ml of concentrated sulfuric acid was added, and the mixture was stirred for 5 min. Hexamethyldisilizane (100 ml, 0.48 mol) and trimethylsilyl chloride (1.0 ml, 0.008 mol) were added and ammonia gas was evolved vigorously. After stirring for ~25 min the reaction mixture was a clear yellow solution. It was cooled to 0 °C and toluene (500 ml) was added. The mixture was extracted with 500 ml and then 200 ml of 10% aqueous potassium carbonate and the aqueous phases back-extracted with 100 ml of toluene. The total toluene was dried over magnesium sulfate, stirred with 2.0 g of activated carbon for 15 min, filtered, washed, and concentrated to a total weight of 160 g. Hexane (700 ml) was added and the semisolid dissolved upon warming to 65 °C. The solution was slowly cooled with stirring to 0 °C; the crystals were collected by filtration, washed with hexane–toluene (9:1), and dried to give 50.0 g of colorless needles (79%), mp 129.5–130 °C. The NMR spectrum (CCl_4) showed the following: τ 3.63 (2 H, broad peak, 2 NH), 4.28 (1 H, doublet, J = 5.5 Hz, C_1 proton), 5.50 (1 H, doublet, J = 5.5 Hz, C_2 proton), 5.81 (1 H, partially resolved triplet, J = 0.8 Hz, C_3 proton), 6.2–6.7 (3 H, multiplet, C_4 proton and C_5 methylene group), 9.83 and 9.95 (each 9 H, two singlets, 2 $SiMe_3$ groups).

***cis*-β-Trimethylammoniumacrylonitrile Tosylate (IVc).** Into a 1.0-l. jacketed, three-necked flask was added a THF solution of potassium *tert*-butoxide (273 g, 55.4 g of KO-*t*-Bu, 495 mmol; this material had been assayed as 20.3% KO-*t*-Bu, 0.40% KOH, 0.9103 g/ml). The solution was cooled to −45 °C and then a solution of isoxazole (Rayco Chemical Co., 27.60 g, 400 mmol) in dry THF (50 ml) was added dropwise at such a rate that temperature was maintained at −39 °C or lower (addition took 31 min). After approximately 5 min of addition, a white precipitate of the enolate salt developed and by the end of the addition the mixture was a thick slurry. The slurry was stirred for 30 min further at −40 to −45 °C. Solid tosyl chloride (92.5 g, 485 mmol) was added in portions at such a rate that the temperature stayed below −38 °C (required ca. 13 min to add) and the white suspension turned black. Acetonitrile was added (300 ml) dropwise over 6 min and the temperature stayed at −43 °C. After stirring overnight at −10 °C, the mixture was concentrated to a small volume (131 g), 750 ml of toluene was added, and the mixture was extracted with 2 × 500 ml of 5% Na_2CO_3. This was back extracted with 100 ml of toluene. (Note: the backwash gave an emulsion and was filtered to remove a black solid.) The toluene extracts were combined, dried over sodium sulfate, and stirred with 10 g of activated carbon for 30 min. This was filtered and washed well to give a pale brown solution of enol tosylate VII. The isomer ratio can be determined readily at this point by running an NMR of an aliquot of the toluene solution. The ratio of VIIc and VIIt is ca. 95:5. The toluene solution was concentrated to 1000 g and stirred at 35–40 °C. A solution of trimethylamine (50 ml, 32.8 g, 560 mmol) in 150 ml of cold toluene was added dropwise over ~30 min. During this addition crystals of cis quaternary salt IVc precipitated. The slurry was stirred for 2 h at room temperature, filtered, and washed with 75 ml of toluene, 75 ml of 2:1 toluene–methylene chloride, then 2× 75 ml of pentane, and dried to give 106.1 g of off-white solid (94%), mp 138–145 °C. This material was suitable for further reactions. Purest cis tosylate VIIc can be obtained by crystallization of the tosylate prior to addition of trimethylamine. After crystallization from methylene chloride–hexane, a white solid is obtained, mp 96.5–97 °C. Pure VIIc caused skin irritation on one occasion and should be handled cautiously. Conversion of this to the cis quaternary salt IVc gave a snow-white, crystalline solid, mp 152.5–154 °C. The NMR spectrum of pure IVc (Me_2SO-d_6) showed the following: τ 2.3–3.0 (5 H, multiplet, aromatic protons and proton on corbon β to cyanomoiety), 3.45 (1 H, doublet, J = 10 Hz, proton on carbon α to the cyano moiety), 6.45 (3 H, singlet, protons on the toluene methyl group).

2,2′-Anhydro-1-β-D-arabinofuranosylcytosine Tosylate (IIIa TsOH CH_3CN). A mixture of oxazoline Ia (13.051 g, 75 mmol), cis quaternary salt IVc (25.4 g, 90 mmol), and 75 ml of DMF was stirred at 50 °C for 10.5 h with a nitrogen sparge at 1 ft^3/min and through a DMF bubbler to presaturate the nitrogen with DMF. Acetonitrile (300 ml) was added rapidly and the solution was seeded to develop crystals of IIIa. The slurry was slowly cooled to room temperature over 30 min, then to 0 °C and stirred for 1 h at 0 °C. The crystals were collected by filtration and washed with 2 × 20 ml of acetonitrile–DMF (9:1), then 2 × 25 ml of acetonitrile and dried under vacuum to give 23.30 g (71%) of white solid. Melting point determinations were meaningless because the material first lost the acetonitrile (of solvation), then decomposed from 90 to 110 °C. The NMR spectrum (Me_2SO-d_6) showed the following: τ 0.8 (1 H, broad peak, NH or OH), 1.72 [1 H, doublet, J = 7 Hz, olefinic proton (probably C-6)], 2.4–2.8 (4 H, multiplet, aromatic protons of the tosylate moiety), 3.39 [2 H, 2 doublets, J = 6 and 7 Hz, proton on C_1 of sugar, and olefinic proton (probably C-7)], 3.9 (1 H, broad peak, NH or OH), 4.53 (1 H, doublet, J = 6 Hz, C_2 proton), 4.95 (1 H, broad peak, NH or OH), 5.47 (1 H, singlet, C_3 proton), 5.71 (1 H, singlet, C_4 proton), 6.55 (3 H, poorly resolved multiplet, OH or NH, and C_5 methylene proton), 7.71 (3 H, protons on the toluene methyl group), 7.95 (5 H, acetonitrile protons). Those signals assigned to NH or OH were shown to disappear by addition of deuterium oxide followed by redetermination of the NMR spectrum. A sample of authentic 2,2′-anhydro-1-β-D-arabinofuranosylcytosine hydrochloride prepared by the method of Sanchez[1] showed the following NMR spectrum (Me_2SO-d_6) after admixture with deuterium oxide: τ 1.70 [1 H, doublet, J = 7 Hz, olefinic proton (probably C_6)], 3.38 [2 H, 2 doublets, J = 6 and 7 Hz, proton on C_1 and olefinic proton (probably C_7)], 4.55 (1 H, doublet, J = 6 Hz, C_2 proton), 5.45 (1 H, singlet, C_3 proton), 5.70 (1 H, broadened singlet, C_4 proton), 6.55 (2 H, broad singlet, C_5 methylene protons).

1-β-D-Arabinofuranosylcytosine (AFC). Tosylate salt IIIa $TosOHCH_3CN$ (8.002 g, 18.25 mmol) and 80 ml of 2 N ammonium hdroxide were stirred at 58 °C for 80 min. The solution was concentrated to a weight of 40 g and added to a Dowex MSC-1 resin column (1.5 × 28 cm, 20–50 mesh, H^+ form, 55 ml of resin equivalent to 94 mequiv): loading phase, 40 g of solution and 2 × 5 ml of water all at 1.0 ml/min flow rate (fraction 1); wash phase, 80 ml of water at 1.0 ml/min (fraction 2, 80 ml); elution phase, 4.5 N ammonium hydroxide at 1.0 ml/min (fraction 3, 35 ml; fraction 4, 125 ml; and fraction 5, 20 ml). TLC analysis indicated that AFC was present only in fraction 4; uv analysis of fraction 4 indicated 101% of the theoretical amount of AFC (4.52 g). Fraction 4 was concentrated to 40 g, 100 ml of methanol was added, and the solution was stirred with 0.50 g of activated charcoal for 30 min. The mixture was filtered and the carbon washed with methanol–water (70:30). The filtrate was concentrated to 9.40 g; 3.0 ml of methanl was added and the mixture warmed to 85 °C to achieve complete solution. This was slowly diluted with 90 ml

of methanol at reflux over 1.5 h. The crystal slurry was cooled to 0 °C over a period of 1.5 h, and stirred at 0. °C for 1 h. The crystals were collected by filtration, washed and dried to give 3.567 g of crystalline AFC. From concentration of the mother liquors a second crop of AFC was obtained, 0.45 g, to give a total yield of 90% from IIIa $TosOHCH_3CN$.The first and second crops of AFC were shown to be identical with authentic AFC by ir, uv, TLC, elemental analysis, and optical activity.

Equilibrium Mixture of *cis*- and *trans*-β-Tosyloxyacrylonitrile (VIIIc and VIIt). To a stirred solution of sodium methoxide (5.35 g, 99 mmol) in reagent 2-propanol (120 ml) was added dropwise over 15 min isoxazole (6.90 g, 100 mmol) and this was stirred under nitrogen for 1 h. The slurry was concentrated to dryness and suspended in 100 ml of acetone at 0 °C and a solution of recrystallized tosyl chloride (17.80 g, 94 mmol) in 50 ml of acetone was added dropwise over 30 min. The mixture was stirred at 25 °C overnight, concentrated to dryness, added to 500 ml of benzene, and extracted with 2 × 50 ml of 10% potassium bicarbonate, then with 250 ml of 25% aqueous sodium chloride. The aqueous phases were back extracted with 2 × 250 ml of benzene. The total benzene extracts were dried ($MgSO_4$) and concentrated to a solid, 21.64 g (97% crude). *Caution:* The crude mixture as well as the crystalline compounds described below easily cause a rash and are skin irritants.

Chromatographic Separation of VIIc and VIIt. A mixture (2:1) of VIIc:VIIt (30.5 g) was mixed with 60 g of silica gel (G. F. Smith Co., which had been deactivated by the addition of 6% water) in ethyl acetate and the mixture concentrated to dryness. This was added to a column of silica gel–6% water (1440 g, 6 × 80 cm) packed in cyclohexane–ethyl acetate (95:5). Elution was continued with 1.5 l. of 95:5, 2.0 l. of 90:10, then 16 l. of 85:15 cyclohexane–ethyl acetate and the progress of the chromatography was followed by TLC (silica gel GF, with 3:1 benzene–ethyl acetate). The earlier 7 l. of the 85:15 system contained pure trans VIIt; this was concentrated to give 9.4 g of the pure trans VIIt. The latter 8 l. of the 85:15 system contained cis VIIc. This was concentrated to give 18.5 g of pure VIIc. Tosylate VIIc was crystallized from ethyl acetate–hexane, mp 94.0–95.5°C. Tosylate VIIt was crystallized from methylene chloride–hexane, mp 87–88.5 °C. The NMR spectra ($CDCl_3$) showed the following. VIIc: τ 2.18–2.6 (4 H, multiplet, aromatic protons), 2.75 (1 H, doublet, J = 6.5 Hz, assigned to olefinic proton on β-carbon atom of the acrylonitrile moiety), 5.02 (1 H, doublet, J = 6.5 Hz, olefinic proton on α carbon of the acrylonitrile moiety), 7.51 (3 H, singlet, protons of the toluene methyl group). VIIt: τ 2.2–2.6 (4 H, aromatic proton), 2.53 (1 H, doublet, J = 12.5 Hz, proton on β carbon), 4.75 (1 H, doublet, J = 12.5 Hz, proton on α carbon), 7.51 (3 H, singlet, protons on the toluene methyl group).

Trans Cyanovinyl Adduct IIb. Oxazoline Ib (3.9776 g, 12.5 mmol), trans tosylate VIIt (3.067 g, 13.75 mmol), 50 ml of dry dioxane, and sodium carbonate (1.541 g, 14.5 mmol) were stirred at 92°C under nitrogen for 19 h. An aliquot (0.050 ml was silylated by stirring with 0.50 ml of bis(trismethylsilyl)trifloroacetamide (BSTFA) for 1 h at 25°C. This was analyzed by GLC (F & M Model 800, 210° C, 6 ft 2% SE-30); a trace of tosylate VIIt was present at 0.5 min retention time, 8% of oxazoline Ib $2Me_3Si$ at 1.0 min, and 92% of the trans cyanovinyl adduct IIb Me_3Si at 4 min.

The reaction mixture was cooled to 15°C, and trimethylamine–tetrahydrofuran (THF) (1.80 ml, 2.0 N) was added to destroy the excess trans tosylate VIIt. After the mixture was stirred for 40 min, it was filtered and the residue washed with THF. The filtrate was concentrated to a brown glass (4.274 g). An NMR spectrum ($CDCl_3$) showed the following: τ 2.45 (1 H, doublet, J = 14.5 Hz, assigned to the olefinic proton on the β-carbon atom of the acrylonitrile moiety), 4.13 (1 H, doublet, J = 5.5 Hz, proton at C_1 of the sugar moiety), 4.90 (1 H, doublet, J = 14.5 Hz, olefinic proton on the α-carbon atom of the acrylonitrile moiety), 5.16 (1 H, doublet, J = 5.5 Hz, proton at C_2), 5.60 (1 H, broadened singlet, proton at C_3), 5.8 (1 H, broadened singlet, proton at C_4), 6.2–6.6 (2 H, multiplet, methylene protons at C_5), 9.81 and 9.90 (9 H each, two singlets, protons on the trimethylsilyl groups).

Reaction of Oxazoline Ib with Propiolonitrile to Form the Cis-Cyanovinyl Adduct Vb. Oxazoline Ib (80 mg, 0.25 mmol) in 0.40 ml of $CDCl_3$ was stirred at room temperature for 2 h after addition of propiolonitrile (14.7 mg, 0.29 mmol). The NMR spectrum ($CDCl_3$) showed the following: τ 2.80 (1 H, doublet, J = 10.5 Hz, olefinic proton on the β-carbon atom of the acrylonitrile moiety), 3.44 (1 H, doublet, J = 5.5 Hz, proton at C_1 of the sugar moiety), 4.1–4.3 (2 H, broad peak, NH), 5.23 (1 H, doublet, J = 5.5 Hz, proton at C_2), 5.43 (1 H, doublet, J = 10.5 Hz, olefinic proton at the α carbon), 5.55 (1 H, broadened singlet, proton at C_3), 5.85 (1 H, multiplet, proton at C_4), 6.3–6.8 (2 H, multiplet, methylene protons at C_5), 9.87 and 9.95 (9 H each, two singlets, protons on the trimethylsilyl groups). An aliquot of this NMR sample (0.020 ml) and 0.50 ml of BSTFA was stirred at 25 °C for 1 h. This sample was analyzed by GLC: trace of oxazoline I at 1.0 min, and major peak at 2.5 min retention time corresponding to Vb Me_3Si.

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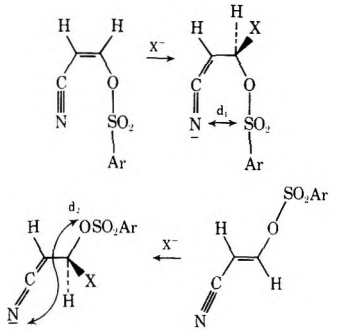
Registry No.—Ia, 36994-58-8; Ib, 58311-70-9; IIb, 58311-71-0; IIIa TsOH, 58342-55-5; IVc, 58311-73-2; Vb, 58342-56-6; *cis*-VII, 58311-74-3; *trans*-VII, 58311-75-4; AFC, 147-94-4; D-arabinose, 10323-20-3; cyanamide, 420-04-2; isoxazole, 288-14-2; tosyl chloride, 98-59-9; propiolonitrile, 107-13-1.

References and Notes

(1) D. H. Shannahoff and R. A. Sanchez, *J. Org. Chem.*, **38**, 593 (1973), & references cited therein.
(2) L. Claisen, *Chem. Ber.*, **25**, 1787 (1892).
(3) F. Scotti and E. J. Frazza, *J. Org. Chem.*, **29**, 1800 (1964).
(4) We prepared β-chloroacrylonitrile by the method described in ref 3, but found it too irritating to our skin to be handled conveniently. Further work with it was then discontinued.
(5) D. E. Jones, R. D. Morris, C. A. Vernon, and R. F. M. White, *J. Chem. Soc.*, 2349 (1960).
(6) Professor J. E. Baldwin recently suggested to me a plausible explanation for the difference in reactivity of the cis tosylate VIIc and the trans tosylate VIIt based on dipole–dipole interactions of the sulfonyl and nitrogen moieties in the molecules.



Since d_2 > d_1 trans reacts much faster than cis

(7) GLC-mass spectra were all run on a CH-7 mass spectrometer.
(8) Sanchez[1] had used DMAC as the solvent in his studies and we used DMF, Me_2SO, or chloroform. We do not think that the different solvent used in Sanchez's case made any difference, however, because his cyanovinyl adduct (corresponding to II) cyclized so readily; this indicates again that his cyanovinyl adduct was cis.
(9) Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. NMR spectra were recorded on a Varian A-60A spectrometer and reported values are relative to tetramethylsilane.

Selective Formation of 2 Esters of Some Methyl α-D-Hexopyranosides via Dibutylstannylene Derivatives

Raphael M. Munavu and H. Harry Szmant*

Department of Chemistry, University of Detroit, Detroit, Michigan 48221

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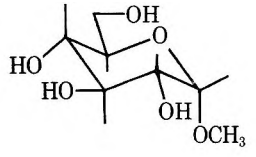
Selective esterification of several methyl D-hexopyranosides by means of base-catalyzed transesterification, *N*-acylimidazoles, and dibutylstannylene derivatives of the carbohydrates revealed the last mentioned method to be most effective when dealing with the α-pyranosides. The NMR spectra and differences in reactivity suggest that the selective formation of C2 esters is associated with a coordination of tin with the α-methoxy group. The selective formation of C2 esters of methyl α-D-gluco-, α-D-allo-, and α-D-galactopyranosides is described even in the presence of the unblocked C6-hydroxyl group.

The primary hydroxyl groups of carbohydrates are considered to be more reactive toward esterification and alkylation than the secondary hydroxyl groups.[1] Consequently, the synthesis of carbohydrates substituted at a secondary hydroxyl group and containing a free primary hydroxyl usually requires the application of blocking–deblocking techniques[2] as well as tedious separation procedures that lower the yields of the desired product. The conversion of methyl α-D-glucopyranoside (1) to methyl 2-*O*-benzoyl-α-D-glucopyranoside (**2a**),[3] for example, or of the corresponding 2-*O*-mesyl and 2-*O*-tosyl esters,[4] required a three-step procedure and the separation from relatively large amounts of the 3 isomers.



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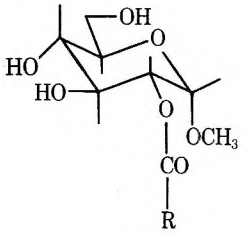

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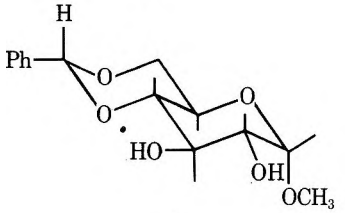


3

a, R = Ph
b, R = $CH_3(CH_2)_{10}$
c, R = $CH_3(CH_2)_{12}$

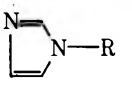
Our interest in isomerically pure monoesters of sugars prompted a search for a more efficient route to 2 esters (e.g., **2**). This paper describes the results of base-catalyzed transesterifications as well as a selective, high-yield process for accomplishing the desired transformation in essentially one step by using the dibutylstannylene intermediates of the carbohydrates.

Results and Discussion

The direct esterification of 4,6-*O*-benzylidene D-hexopyranosides leads to a mixture of 2 and 3 esters depending on the nature of the esterifying reagent (see Table I). When the corresponding benzal derivative of 1 (**3**) was allowed to react with ethyl myristrate under base-catalyzed transesterification conditions there was obtained a mixture of the two monoesters, the diester, and unreacted starting material even though the esterification was limited to only two hydroxyl sites. The analogous transesterification in the presence of potassium methoxide and 18-crown-6 did not affect the ratio of the 2 and 3 esters.

Selective esterification by means of base-catalyzed transesterification is complicated also by the possibility of intramolecular migration of the acyl group. Thus, when the 2-myristate of **3** (**4**) was heated for ca. 40 h in DMF in the presence of a catalytic amount of solid K_2CO_3, the starting material and the corresponding 3 ester (**5**) were isolated in equal amounts.

In view of the considerable success of acylimidazoles[6] in selective esterification reactions,[7] we allowed **2** to react with **6** in refluxing chloroform for a period of 16 h. It was found that

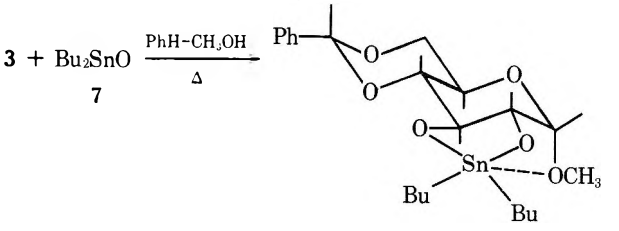


6

a, R = PhCO
b, R = $CH_3(CH_2)_{12}CO$
c, R = p-CH_3PhSO_2
d, R = $CH_3(CH_2)_{10}CO$

the initially formed 2 esters were subect to imidazole-catalyzed isomerization and longer reaction times (30–40 h) led to varying amounts of the 2 and 3 esters. Methyl 4,6-*O*-benzylidene-β-D-glucopyranoside and methyl 4,6-*O*-benzylidene-α-D-mannopyranoside could not be selectively esterified by means of this procedure.[7f,9]

Di-*n*-butyltin oxide (**7**) was recently used for the selective introduction of a tosyl group at the 2′-OH group of nucleosides.[8] We have found that an equimolar mixture of **3** and **7** upon heating in methanol–benzene (1:10) for 45 min gave a crystalline material (**8**) which was isolated upon the removal of the solvents in vacuo. The elemental analysis and NMR



7 8

spectrum were consistent with the structure of methyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α-D-glucopyranoside (**8**). The chemical shifts of representative protons in **3** and **8** are given in Table II. The chemical shift differences between **3** and **8** are attributed to (a) the deshielding of the anomeric hydrogen and of the C1 methoxy group because of a coordination between the C1 methoxy group and tin as suggested in **8**; and (b) a conformational change in the dioxane ring induced by the tendency of the five-membered stannylene ring to approach coplanarity.

When **8** was treated at room temperature with a dioxane solution of benzoyl chloride in the presence of triethylamine the 2-benzoate was isolated in 85% yield. Similarly it was possible to prepare the 2-myristate (**4**), the 2-laurate, and the 2-*O*-tosylate in good yields (70–90%). In the case of the car-

Table I. Selective Esterification of 4,6-O-Benzylidene D-Hexopyranosides

Compd	Conditions[e]	2 ester, %	3 ester, %	2,3 diester, %	Ref
α-D-Glucoside	A	24	6	35	*a*
	B	13	25	9	*a*
	C	25	20	10	*b*
	D	82	0	0	*b*
	D′	93	7	0	*b*
	E	92	1	0	*b*
	E	94	1	0	*b*
	F	62	0	0	*d*
β-D-Glucoside	C	26	34	0	*b*
	D	30	35	0	*b*
	E′	30	20	0	*b*
α-D-Mannoside	A	19	20	33	*c*
	C	37	32	3	*b*
	D	50	50		*d*
	F	57	25		*d*
	E′	25	35		*b*
α-D-Galactoside	E″	64	0	0	*b*
α-D-Alloside	E′	91	0	0	*b*

[a] R. W. Jeanloz and D. A. Jeanloz, *J. Am. Chem. Soc.*, 79, 2579 (1957). [b] This work. [c] R. W. Jeanloz and D. A. Jeanloz, *J. Am. Chem. Soc.*, 80, 5692 (1958); [d] S. A. Abbas and A. H. Haines, *Carbohydr. Res.*, 39, 358 (1975). [e] A, PhCOCl, C_5H_5N; B, $(PhCO)_2O$, C_5H_5N; C, $CH_3(CH_2)_{12}CO_2Et$, K_2CO_3; D, PhCO–imidazole, $CHCl_3$; D′, $CH_3(CH_2)_{12}CO$–imidazole, $CHCl_3$; E, Bu_2SnO, $CH_3(CH_2)_{12}COCl$, Et_3N; E′, Bu_2SnO, PhCOCl, Et_3N; E″, Bu_2SnO, *p*-TsCl, Et_3N; F, PhCOCN, Et_3N.

Table II. NMR Parameters for Some Protons in 3 and 8 in $CDCl_3$[a]

Compd	δ PhC(=O)—H	—C(=O)—H (MeO)	—C—OCH₃
3	5.52 (s)	4.75 (d) ($J_{1,2}$ = 3.5 Hz)	3.38 (s)
8	5.45 (s)	4.85 (d) ($J_{1,2}$ = 3.0 Hz)	3.45 (s)

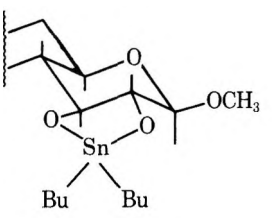
[a] δ(Me_4Si) 0.

boxylic acid esters, the reaction was complete in 5–15 min, while the formation of the tosylate turned out to be much slower (3–5 h). During the formation of the 2-laurate there was isolated 3% of the 3-laurate.

Acylation of the analogous tin derivatives of methyl β-D-glucopyranoside and methyl α-D-mannopyranoside failed to be selective. In each case there were obtained approximately equal amounts of the 2 and 3 esters in addition to a rather high recovery of the starting sugars. The explanation for this difference in behavior may be in the inability of the respective tin compounds **9** and **10** to give coordination between the metal and the α-methoxy group as suggested in the case of **8**. This explanation is consistent with the fact that the tin compound of methyl 4,6-*O*-benzylidene-α-D-galactopyranoside (**11**) again give the 2-tosylate selectively when it was treated with *p*-toluenesulfonyl chloride and triethylamine. Likewise the methyl 2-*O*-benzoyl-α-D-allopyranoside was prepared in 90% yield when methyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α-D-allopyranoside was treated with benzoyl chloride in the presence of triethylamine.

Selective esterification brought about by means of dibutylstannylene derivatives was next investigated using the free, unprotected sugars.

The reaction of equimolar amounts of dibutyltin oxide and methyl α-D-glucopyranoside (**1**) in methanol gave a quantitative yield of **12** and the latter was then converted to the



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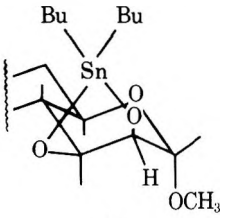

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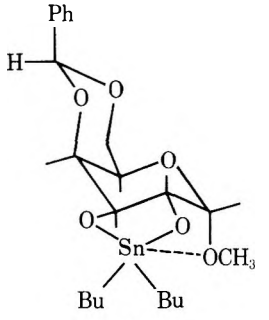

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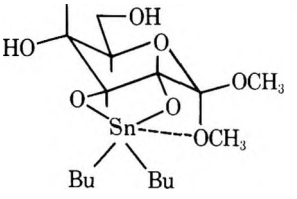

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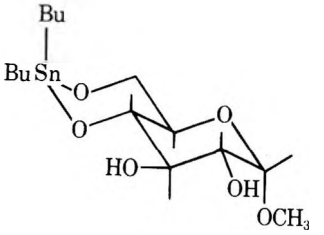
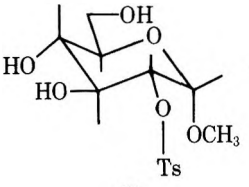
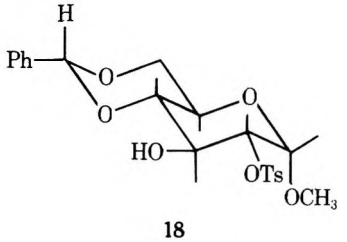


13

methyl 2-*O*-benzoyl-α-D-glucopyranoside in 80–90% yield by means of a subsequent reaction with benzoyl chloride in the presence of triethylamine. Similarly, **12** and myristoyl chloride or *p*-toluenesulfonyl chloride gave the corresponding 2 esters. The 6 esters could not be detected by TLC in any of the above cases, but the 2,6 diester was sometimes present in 1–2% yield. Since the 2-tosylate of **1** (**17**) resisted crystallization, it was characterized by conversion to the known, crystalline, 4,6-*O*-benzylidene compound (**18**).



17

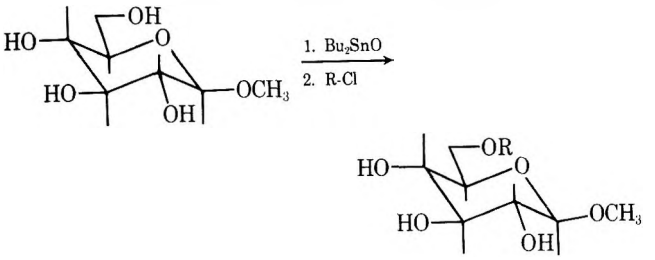


18

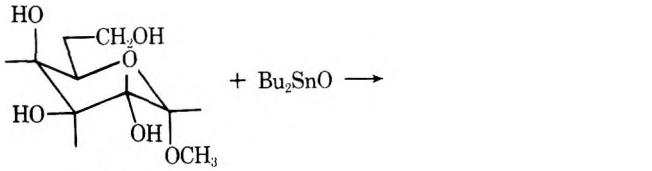
The fact that the 2 esters were formed in the presence of the "more reactive" primary C6-OH suggests that the dibutylstannylene of **1** has the structure **12** rather than **13**. The presumed preference for the formation of the five-membered stannylene ring could be due to the favorable semiequatorial conformation of the *gem*-di-*n*-butyl groups, whereas one of these bulky groups would be forced into an unfavorable axial conformation in the case of the six-membered compound **13**. A similar rationale is sometimes offered[10] to explain the great tendency of acetone to form the five-membered dioxolanes with glucose, while benzaldehyde favors the six-membered dioxanes. Unfortunately this hypothesis could not be tested, so far, owing to the hydrolytic instability of the tin compounds.

Structure **12** may also be favored over **13** because of the additional coordination of tin with the C1 methoxy group.

By contrast, methyl β-D-glucopyranoside could not be selectively esterified at position 2 under the conditions successful with its α anomer **1**. In fact, only the 6 esters were obtained (~80% yield) when the material obtained by treatment of methyl β-D-glucopyranoside with **7** was treated with either *p*-toluenesulfonyl, benzoyl, or myristoyl chlorides. On the



a, R = PhCO
b, R = $CH_3(CH_2)_{12}CO$
c, R = *p*-CH_3PhSO_2



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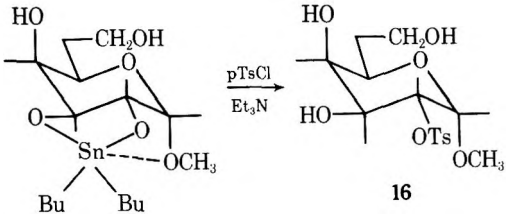


15 **16**

other hand, methyl α-D-galactopyranoside (**14**) was easily converted to 2-tosylate **16** via the tin compound presumed to have the structure **15**. The syrupy **16** was characterized by its conversion to the known crystalline methyl 2-*O*-tosyl-4,6-*O*-benzylidene-α-D-galactopyranoside using a DMF solution of benzaldehyde diethyl acetal in the presence of *p*-TsOH catalyst.

In conclusion, the method described here for the selective preparation of 2 esters of methyl α-D-gluco-, α-D-galacto-, and α-D-allopyranosides illustrates an extremely useful application of organotin alkoxides in organic synthesis.[11] Its success appears to depend on the selective reactivity at the C2-O when the 2,3-stannylene intermediate is capable of coordination between the α-methoxy group and tin. Work is in progress to extend this selective esterification method to disaccharides such as sucrose.

Experimental Section

Melting points were determined by means of a Mel-Temp apparatus and are uncorrected. TLC was carried out on silica gel G coated plates and detection was effected by charring with 50% H_2SO_4. NMR spectra were recorded at 60 MHz with a Varian A-60A spectrometer using Me_4Si as an internal standard. Ir spectra were recorded as KBr pellets with a Perkin-Elmer Model 475 spectrometer. Elemental analyses were carried out by M-H-W Laboratories, Garden City, Mich.

Methyl 2,3-*O*-Dibutylstannylene-α-D-glucopyranoside (12). Dibutyltin oxide (12.50 g, 50 mmol) was added to a solution of methyl α-D-glucopyranoside (**1**, 9.7 g, 50 mmol) in methanol (200 ml) and the resulting milky solution was refluxed until it became homogeneous and clear (45 min). After refluxing for an additional 0.5 h, the solvents were evaporated in vacuo to leave a white solid, mp range 105–115 °C. Anal. Calcd for $C_{15}H_{30}O_6Sn$: C, 42.12; H, 7.06. Found: C, 41.63; H, 7.18.

Methyl 2-*O*-Myristoyl-α-D-glucopyranoside (2c). A. Methyl 2,3-*O*-dibutylstannylene-α-D-glucopyranoside (**12**, 4.25 g, 10 mmol) in dioxane (75 ml) was treated with triethylamine (1.54 ml, 11 mmol) followed by a slow addition (5 min) of myristoyl chloride (2.71 g, 11 mmol) in dioxane (10 ml). After 1 h at room temperature, TLC (ethyl acetate, silica gel G) indicated the absence of starting material and the presence of a major spot at R_f 0.55 and of a minor spot at R_f 0.78. After stirring for an additional 1 h, the salts were filtered and washed with dioxane (15 ml). Evaporation of the combined filtrates in vacuo gave a syrup which was passed through a column of silica gel G (200 g) using ethyl acetate as the eluent. The fractions containing the 2-*O*-myristoyl derivative were combined and crystallized from ethyl acetate–petroleum ether (bp 30–60 °C) at 5 °C to give a white solid (2.95 g, 73%) mp 94–96 °C, mmp (with product prepared as in B below) 94–97 °C. Anal. Calcd for $C_{21}H_{40}O_7$: C, 62.38; H, 9.90. Found: C, 62.31; H, 9.82.

B. Methyl 2-*O*-myristoyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**4**, 1 g) was hydrolyzed using 75% aqueous acetic acid to give the methyl 2-*O*-myristoyl-α-D-glucopyranoside (**2c**) in 80% yield, mp 95–96 °C, mmp 94–97 °C.

Methyl 2-*O*-Benzoyl-α-D-glucopyranoside (2a). A. To a magnetically stirred, slightly cloudy solution of methyl 2,3-*O*-dibutylstannylene-α-D-glucopyranoside (**12**, 4.25 g, 10 mmol) in dioxane (75 ml) there was added triethylamine (1.54 ml, 11 mmol) followed by slow addition of benzoyl chloride (1.32 ml, 11 mmol). The solution became clear upon addition of the benzoyl chloride but a white precipitate started forming ~2 min later. TLC examination of the solution (ethyl acetate, silica gel G) after 1 h showed the presence of a major spot at R_f 0.50 and a minor spot at R_f 0.70. The salts were filtered and washed with dioxane (20 ml) and the combined filtrates were evaporated in vacuo to leave a syrup which was fractionated on a column of silica gel G (120 g) using ethyl acetate as eluent. The first compound eluted from the column was methyl 2,6-di-*O*-benzoyl-α-D-glucopyranoside (0.08 g, ~2%), mp 139–140 °C (lit.[3] 141–142 °C). Anal. Calcd for $C_{21}H_{22}O_8$: C, 62.67; H, 5.51. Found: C, 62.55; H, 5.77.

The second compound eluted from the column was the desired material **2a** (2.05 g, 70%). Crystallization from EtOAc–petroleum ether gave white crystals, mp 179–180 °C, mmp 177.5–178.5 °C (lit.[3] mp 174–175 °C). Anal. Calcd for $C_{14}H_{18}O_7$: C, 56.37; H, 6.04. Found: C, 56.38; H, 6.09.

B. Methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside (1.5 g) was heated at 75–80 °C for 1 h in 75% aqueous acetic acid. The solvents were then removed in vacuo and the white residue was dissolved in hot ethyl acetate to which light petroleum ether (bp 30–60 °C) was added until crystallization started. The white crystals which were collected (1.10 g, 98%) had mp 177–178.5 °C and mmp 177.5–179 °C.

Methyl 4,6-*O*-Benzylidene-2,3-*O*-dibutylstannylene-α-D-glucopyranoside (8). A mixture of **3** (8.50 g, 30 mmol) and dibutyltin oxide (7.70 g, 30 mmol) was refluxed in benzene–methanol (150–15 ml) until the solution became clear (~45 min). It was then left at 50–55 °C for 14 h and then the solvents were removed in vacuo to leave a white solid (14.5 g, 91%), mp 194–195 °C. Anal. Calcd for $C_{22}H_{34}O_6Sn$: C, 51.50; H, 6.60. Found: C, 51.35; H, 6.69.

Methyl 4,6-*O*-Benzylidene-2-*O*-tosyl-α-D-glucopyranoside. Triethylamine (1.44 ml) was added to the tin compound **8** (5.14 g) in dioxane (100 ml) followed by *p*-TsCl (1.90 g) in dioxane (20 ml). The solution was stirred overnight and then the undissolved salts were filtered and washed with dioxane. The syrup obtained on evaporation of the solvent in vacuo was dissolved in hot ethyl acetate and light petroleum ether was added to initiate crystallization. The product was collected as white needles (3.05 g, 70%), mp 153–154 °C (lit.[12] mp 153–154 °C).

Methyl 2-*O*-Benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside. A. Triethylamine (1.44 ml) was added to the tin compound **8** (5.14 g, 10 mmol) dissolved in dioxane (100 ml). Benzoyl chloride (1.20 ml, 10 mmol) in dioxane (20 ml) was then slowly added to the cooled (~5 °C) mixture. The solution was stirred for 6 h at ambient temperature and the solids filtered. The solvent was evaporated to leave a syrup which was dissolved in hot ethyl ether to which was slowly added petroleum ether (bp 30–60 °C) until milky. Crystals of the title compound were collected after 16 h at 5 °C, mp 168–170 °C (3.35 g, 86%).

B. The tin compound **8** was prepared in situ by refluxing a solution of **3** (1.41 g, 5 mmol) and dibutyltin oxide (1.25 g, 5 mmol) in dry methanol (50 ml) for 45 min. After the solution was cooled to 5 °C, triethylamine (3.5 ml, 25.0 mmol) was added at once followed by slow addition of benzoyl chloride (3.0 ml, 25 mmol). TLC examination of the reaction mixture after 5 min indicated the presence of a single spot at R_f 0.70 (ethyl ether–petroleum ether, 2:1 v/v). After 2 h at ambient

temperature, the solvents were removed in vacuo, the resulting residue was dissolved in acetone, and the triethylamine hydrochloride was filtered. Evaporation of the acetone extract left a syrupy material which was placed on a silica gel G column (120 g) and eluted with ethyl ether–petroleum ether (2:1 v/v). The first fractions collected contained methyl benzoate. The second compound eluted from the column was the desired material (1.32 g), mp 165 °C. Crystallization from ethyl ether–petroleum ether gave the pure compound as needles, mp 173.5–175 °C (lit.[13] mp 169–170 °C). Anal. Calcd for $C_{21}H_{22}O_7$: C, 65.28; H, 5.70. Found: C, 65.20; H, 5.89.

Lastly, the unreacted starting sugar **3** was eluted from the column (0.27 g). The reaction occurred with 81% conversion and the yield was 85%.

Methyl 4,6-*O*-Benzylidene-2-*O*-tosyl-α-D-galactopyranoside. Methyl α-D-galactopyranoside (**14**, 9.7 g) was refluxed with Bu_2SnO (12.5 g) in MeOH (170 ml) for 1.5 h. Evaporation of the MeOH in vacuo at 50 °C left a glassy solid (**15**), mp 75–85 °C. Anal. Calcd for $C_{15}H_{30}O_6 \cdot H_2O$: C, 40.83; M, 7.04. Found: C, 40.63; H, 7.22. Methyl 2,3-*O*-dibutylstannylene-α-D-galactopyranoside (**15**, 3.20 g) in dioxane (50 ml) was treated successively with Et_3N (1.2 ml) and *p*-TsCl in dioxane (10 ml). After 1 h at ambient temperature TLC indicated the presence of a major spot at R_f 0.20 (EtOAc) and a minor spot at the origin. The reaction was complete after 6 h at 25 °C. The salts were filtered and washed, and the filtrates were evaporated under diminished pressure to leave a syrup which resisted crystallization. Treatment of the syrup (1.20 g) with benzaldehyde diethyl acetal (5 ml) in DMF (10 ml) and a catalytic amount of *p*-toluenesulfonic acid monohydrate for 16 h followed by neutralization of the acid (solid K_2CO_3) and evaporation of the solvents left a syrup which was crystallized from ethyl acetate to give needles, mp 176–178 °C (lit.[14] mp 179–180 °C). Anal. Calcd for $C_{21}H_{24}O_8S$: C, 57.80; H, 5.51; S, 7.34. Found: C, 58.00; H, 5.60; S, 7.50.

Methyl 4,6-*O*-Benzylidene-2-*O*-lauroyl-α-D-glucopyranoside. A. Triethylamine (0.7 ml) was added to a stirred solution of **8** (2.57 g) in dioxane (50 ml) and this was followed by slow addition of 1.0 g (10 ml) of lauroyl chloride. After 40 min at ambient temperature the solid salts were filtered and washed with dioxane (10 ml). The combined solvents were evaporated to leave a white residue which was placed on a column of silica gel and eluted with ether–petroleum ether (1:1 v/v). The 2-*O*-lauroyl derivative of **3** was eluted first (1.26 g, 81%), mp 87–89 °C. Anal. Calcd for $C_{26}H_{40}O_7$: C, 67.46; H, 8.62. Found: C, 67.92; H, 9.07. The second fraction from the column was the 3-laurate (0.06 g, 3%), mp 115–117 °C. Anal. Calcd for $C_{26}H_{40}O_7$: C, 67.46; H, 8.62. Found: C, 67.80; H, 8.97. A portion of unreacted **3** (0.50 g) was recovered.

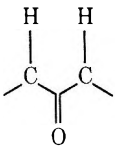
B. Lauroylimidazole [**6d**, R = $CH_3(CH_2)_{10}CO$] was prepared from imidazole (0.68 g, 0.01 mol), dissolved in reagent grade $CHCl_3$ (10 ml), and lauroyl chloride (1.1 g, 0.005 mol) added dropwise to the magnetically stirred solution kept at 10 °C. The resulting white suspension was filtered and the filtrate (containing *N*-lauroylimidazole) was added to **3** (1.41 g, 0.005 mol) in $CHCl_3$ (20 ml). After the mixture was refluxed for 20 h the solution was cooled and extracted successively with 5% bicarbonate (20 ml) and saturated NaCl (2 × 10 ml). After drying over Na_2SO_4 the $CHCl_3$ solution was evaporated to leave 2.2 g of product and this was separated on a column of silica gel using ether–petroleum ether to give the 2-laurate (83%) and the 3-laurate (6.3%).

Methyl 4,6-*O*-Benzylidene-2-*O*-myristoyl-β-D-glucopyranoside by Transesterification. Methyl 4,6-*O*-benzylidene-β-D-glucopyranoside (3.0 g, 11 mmol) was placed in a 100-ml three-neck round-bottom flask containing dry Me_2SO (60 ml), fitted with a magnetic stirring bar, a nitrogen inlet tube, and a rubber septum and connected to a regulated water aspirator. The mixture was heated to 80 °C and then ethyl myristate (2.56 g, 10 mmol) was added, followed by 0.05 g of solid, finely ground K_2CO_3. After 90 h at 80 °C and 60 Torr, the solvent was taken off in vacuo to leave a solid which was extracted with ether. The ethereal extract was washed with 5% NaCl solution, dried (Na_2SO_4), and evaporated to leave 4.5 g of material. This was placed on a column of silica gel (200 g) and eluted using ether–petroleum ether (1:1 v/v). Ethyl myristate was eluted first (1.6 g). Next was eluted the methyl 4,6-*O*-benzylidene-2-*O*-myristoyl-β-D-glycopyranoside. It was crystallized from hexane to give white needles (200 mg), mp 113–115 °C. Anal. Calcd for $C_{28}H_{44}O_7$: C, 68.30; H, 8.94. Found: C, 68.50; H, 8.92.

The corresponding 3-myristate was eluted next and it was similarly crystallized from hexane to give white flakes (270 mg), mp 89–90 °C. Anal. Calcd for $C_{28}H_{44}O_7$: C, 68.30; H, 8.94. Found: C, 68.50; H, 8.77. The methyl 4,6-*O*-benzylidene-β-D-glucopyranoside was eluted last (2.5 g).

Methyl 4,6-*O*-Benzylidene-2-*O*-myristoyl-α-D-glucopyranoside by Transesterification. Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**3**, 6.5 g, 23 mmol) was placed in a 250-ml three-neck flask fitted with a magnetic stirring bar, a nitrogen inlet tube, and a rubber septum and connected to a regulated water aspirator. Dry Me_2SO (120 ml) was added and the mixture was stirred and brought up to 80 °C. After 10 min, ethyl myristate (2.56 g, 10 mmol) was added followed by solid, finely ground potassium carbonate (0.05 g). The water aspirator was regulated to give 60 Torr during the duration of the reaction. After 50 h, the solvent was taken off in vacuo to leave a solid which was equilibrated between ether and water. The ether layer was washed with concentrated NaCl solution, dried (Na_2SO_4), and evaporated to leave a solid which was shown (TLC) to contain **3**, the 2-myristoyl, 3-myristoyl, and 2,3-dimyristoyl derivatives. Separation of the material on column chromatography using petroleum ether–ether (4:1 v/v) as eluent gave ethyl myristate (1.4 g); the 2,3-dimyristate (41 mg), mp 80–82 °C, crystallized from hexane; the 2-myristate (**4**, 615 mg), mp 94–96 °C, crystallized from hexane; and 3-myristate (**5**, 915 mg), mp 121–123 °C, also crystallized from hexane. Compound **3** was eluted last (4.5 g).

The structures of the two monoesters **4** and **5** were deduced from their NMR and ir spectra and by conversion to the corresponding glucopyranosid-3- and -2-uloses using the Pfitzer–Moffatt[5] reagent. Thus the NMR spectrum of the 3-ulose revealed the expected anomeric doublet at δ 5.35 ($J_{1,2}$ = 4.6, $J_{2,4}$ = 1.5 Hz) corresponding to C2 H. The long-range coupling of δ 1.5 Hz is to be expected because the two hydrogen atoms form a symmetrical U relationship around the C3 carbonyl.



On the other hand, the NMR spectrum of the 2-ulose revealed an anomeric singlet at δ 5.28 in agreement with an oxidation at C2.

Base-Catalyzed Equilibration of 4 and 5. Methyl 3-*O*-myristoyl-4,6-O-benzylidene-α-D-glucopyranoside (30 mg) in DMF (5 ml) was kept at 85 °C in the presence of solid K_2CO_3 (10 mg). After 16 h, TLC (ethyl ether–petroleum ether, 1:1) indicated the presence of **4**, **5**, **3**, and some 2,3 diester. Separation was accomplished by preparative TLC: **4** (24%); **5** (24%); **3** (34%); and the diester (18%).

Acknowledgment. We thank M-H-W Laboratories, Garden City, Mich., for the microanalyses.

Registry No.—**1**, 93-30-3; **2a**, 21056-53-1; **2c**, 58463-68-6; **3**, 3162-96-7; **4**, 58463-69-7; **5**, 58463-70-0; **6d**, 3867-67-2; **8**, 58463-75-5; **12**, 58525-83-0; **14**, 3396-99-4; **15**, 58463-76-6; dibutyltin oxide, 818-08-6; methyl 2,6-di-*O*-benzoyl-α-D-glucopyranoside, 26927-44-6; methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside, 28642-64-0; methyl 4,6-*O*-benzylidene-2-*O*-tosyl-α-D-galactopyranoside, 58463-71-1; methyl 4,6-*O*-benzylidene-2-*O*-lauroyl-α-D-glucopyranoside, 33650-78-1; methyl 4,6-*O*-benzylidene-3-*O*-lauroyl-α-D-glucopyranoside, 58463-72-2; methyl 4,6-*O*-benzylidene-2-*O*-myristoyl-β-D-glucopyranoside, 58463-73-3; methyl 4,6-*O*-benzylidene-β-D-glucopyranoside, 14155-23-8; ethyl myristate, 124-06-1; methyl 4,6-*O*-benzylidene-3-*O*-myristoyl-β-D-glucopyranoside, 58463-74-4; lauroyl chloride, 112-16-3.

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Halo Sugar Nucleosides. 5.[1] Synthesis of Angustmycin A and Some Base Analogues

Ernest J. Prisbe, Jiri Smejkal,[2] Julien P. H. Verheyden, and John G. Moffatt*

Contribution No. 122 from the Institute of Molecular Biology, Syntex Research, Palo Alto, California 94304

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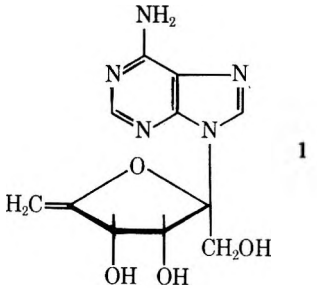
An efficient synthesis of 9-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)adenine (**3**) is described via dehydrohalogenation of 5′-deoxy-5′-iodo-N^6,N^6,$O^{2'}$,$O^{3'}$-tetrabenzoyladenosine (**2c**) with either silver fluoride in pyridine or with DBN in DMF. The synthesis of 1,3,4-tri-*O*-benzoyl-6-deoxy-6-iodo-D-psicofuranosyl bromide (**9**) was achieved starting with D-fructose via oxidation of the 1,2:4,5-di-*O*-isopropylidene derivative followed by borohydride reduction, acid-catalyzed isomerization to the psicofuranose derivative, and iodination by several different routes. Condensation of **9** with several derivatives of adenine provides the 9-(1,3,4-tri-*O*-benzoyl-6-deoxy-6-iodo-β-D-psicofuranosyl) nucleosides (**11**) together with lesser amounts of the α anomers **12**. Dehydrohalogenation of **11** followed by deblocking provides a total synthesis of the nucleoside antibiotic angustmycin A (**1**). Related sequences starting with condensations of **9** with cytosine or 3-methoxycarbonyl-1,2,4-triazole lead to the corresponding base analogues of angustmycin A, **16** and **21**. By appropriate manipulation of the intermediates in the above routes, syntheses of the β-D-psicofuranosyl derivatives of cytosine (**25a**) and of 1,2,4-triazole-3-carboxamide (**22**) are also described.

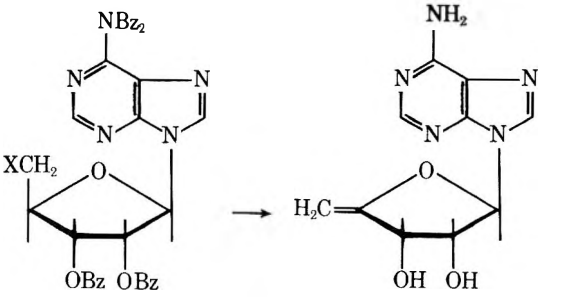
The nucleoside antibiotic angustmycin A,[3] which shows modest antimicrobial[4,6] and antitumor[5] activity, was originally isolated from *S. hygroscopicus* by Yüntsen et al.[6] and an incorrect structure was assigned.[7] Subsequently the antibiotic decoyinine was shown to be identical with angustmycin A, and, based upon spectroscopic evidence, the correct structure was shown to be 9-(6-deoxy-β-D-*erythro*-hex-5-enofuran-2-ulosyl)adenine (**1**).[8]



1

The structure of **1** is interesting since it is the only naturally occurring enofuranosyl nucleoside and at the same time is, together with the closely related antibiotic psicofuranine,[8] one of the few examples of nucleosides derived from ketose sugars. Considerable work has already appeared concerning the synthesis of ketohexose nucleosides derived from psicose,[9] fructose,[10] and sorbose,[11] and the structure of angustmycin A stimulated our own interest in the synthesis of 4′,5′-unsaturated ribonucleosides.[12] During the course of our work the conversion of psicofuranine to angustmycin A was described by McCarthy et al.[13] The key to this synthesis was the ingenious use of an orthoformate ester for the simultaneous and selective blocking of the 1′-, 3′-, and 4′-hydroxyl groups in the intact psicofuranine molecule. In the present paper we describe a totally different approach to the synthesis of angustmycin A in which the problem of selective protection is resolved in a key carbohydrate intermediate that can be efficiently condensed with a variety of heterocyclic bases, thus allowing the synthesis of analogues of **1**.

As a prelude to the synthesis of **1** itself we have first examined the synthesis of the somewhat simpler 9-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)adenine (**3**). The lability of pent-4-enofuranosides toward acids precluded the use of the 2′,3′-*O*-isopropylidene group for protection of the adenosine sugar moiety. Subsequently, however, it was shown that the 2′,3′-*O*-ethoxymethylidene group could be removed without extensive hydrolysis of the vinyl ether.[13] We preferred to use base labile protecting groups for this purpose, and accordingly fully benzoylated 5′-*O*-trityladenosine giving the N^6,N^6,$O^{2'}$,$O^{3'}$-tetrabenzoate (**2a**)[14] in essentially quantitative yield. This compound was originally considered to be the N^1,N^6,$O^{2'}$,$O^{3'}$-tetrabenzoyl derivative but recent work has shown that fully benzoylated adenosine derivatives have both *N*-benzoyl groups at N^6.[15] Subsequent detritylation of **2a** with hydrogen chloride in chloroform then gave crystalline N^6,N^6,$O^{2'}$,$O^{3'}$-tetrabenzoyladenosine (**2b**) in 86% yield without need for chromatography (cf. ref 14). Iodination of **2b** was readily achieved using methyltriphenoxyphosphonium iodide[16] which gave the crystalline 5′-iodo derivative **2c** in 87% yield after only a 10-min reaction at room temperature. It should be noted that attempted iodination of 2′,3′-*O*-isopropylideneadenosine with this reagent gave only an N^3,5′-cyclonucleoside.[16] Acylation of the adenine ring, however, is known to substantially reduce the tendency of adenosine derivatives to form such cyclonucleosides.[17] Treatment of **2c** with silver fluoride in pyridine, a reaction used extensively in the pyrimidine series,[12] was only modestly successful in effecting dehydrohalogenation. Following debenzoylation with methanolic ammonium hydroxide and ion exchange chromatography on a basic resin[18] crystalline **3** was obtained, but only in 15% overall yield. Much better results were obtained



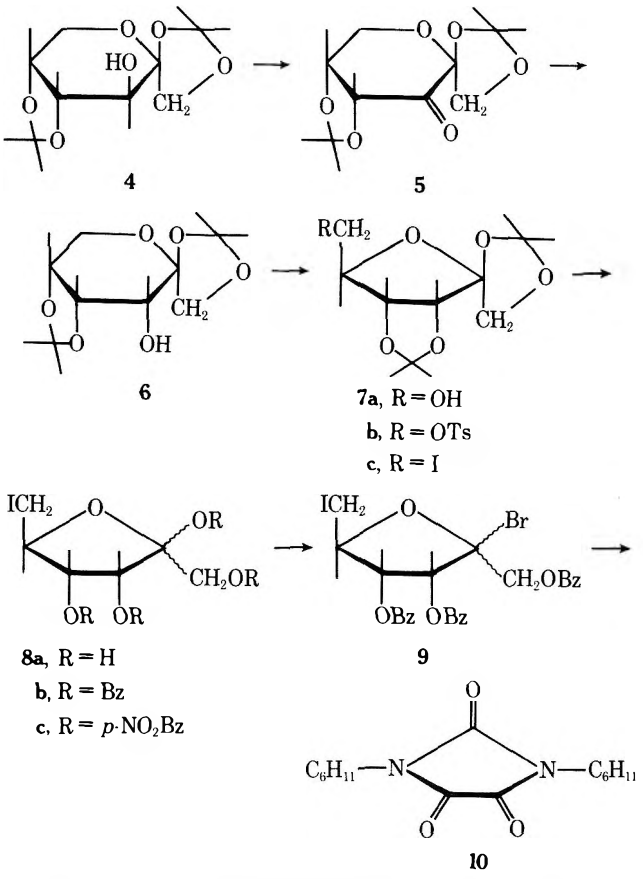
2a, X = Tr
b, X = OH
c, X = I

3

by treatment of **2c** with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in dimethylformamide, the overall conversion to crystalline **3** in this case being 72%. It may be noted that **3** has also been detected as a product from the treatment of coenzyme B_{12} with alkali.[19] The successful synthesis of **3** described above encouraged us to proceed with the planned synthesis of angustmycin A.

Our objective was the synthesis of a derivative of 6-deoxy-6-iodo-D-psicofuranose (e.g., **9**) suitable for condensation with a variety of heterocyclic bases, followed by dehydrohalogenation. While 1,2:3,4-di-*O*-isopropylidene-β-D-psicofuranose (**7a**) can be prepared via the diazo ketone derived from 2,3,4,5-tetra-*O*-acetylribonic acid chloride[9c,20] followed by mild acetonation,[21] a more convenient route involves the oxidation of 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**4**)[22] to the 2,3-hexodiulose **5**[23] followed by stereoselective reduction to 1,2:4,5-di-*O*-isopropylidene-β-D-psicopyranose (**6**)[23] and acid-catalyzed acetal equilibration to the furanose form **7a**.[21b,23b,c,24] We have independently developed this route (**4** → **7a**) although the conditions used for the various steps differ somewhat from those that have been reported. In particular, we have used perchloric acid as the catalyst during preparation of **4** and obtained the pure, crystalline compound in 38% yield on a kilogram scale. The use of perchloric acid gives **4** and its 2,3:4,5-di-*O*-isopropylidene isomer in a ratio of roughly 3:1 by GLC analysis, but homogeneous **4** can be readily obtained by crystallization. The oxidation of **4** to **5** has been examined by others using dimethyl sulfoxide–acetic anhydride[23a,b,d] in yields of 44–70%, and using ruthenium tetroxide.[23c,d] We have done this oxidation using dimethyl sulfoxide and dicyclohexylcarbodiimide in the presence of pyridinium phosphate[25] and have isolated crystalline **5** in 85% yield on a 0.9-mol scale. It is interesting to note that a crystalline by-product of this reaction was isolated in low yield and identified as 1,3-dicyclohexylparabanic acid (**10**).[26] This compound must arise from an unrecognized condensation of dicyclohexylcarbodiimide with oxalic acid, a step that is used to destroy excess carbodiimide.[27] Reduction of the ketone **5** has been examined under a variety of conditions,[23] and we find the use of sodium borohydride in ethanol to be highly stereoselective, affording pure 1,2:4,5-di-*O*-isopropylidene-β-D-psicopyranoside (**6**) in 94% yield. Isomerization of **6** to its furanose isomer **7a** was accomplished using either perchloric or sulfuric acid in acetone and 2,2-dimethoxypropane. While **7a** could be isolated in 62% yield with 98% purity (GLC) by distillation, its crystallization was accomplished only with substantial losses and we have usually preferred to combine this step with suitable derivatization of the 6-hydroxyl group in order to handle crystalline compounds.

Our goal was the preparation of a 6-deoxy-6-iodo-D-psicofuranose derivative (e.g., **9**) which could be condensed with a variety of heterocyclic bases and then dehydrohalogenated to introduce the desired 5′,6′-olefinic function. With this objective in mind we examined a number of methods for the conversion of **7a** into the 6-iodo derivative **7c**. Direct iodination of pure **7a** using methyltriphenoxyphosphonium iodide[16] gave crystalline **7c** in 57% yield but required chromatography on silicic acid. Alternatively, iodination with this same reagent of the crude reaction product from acetonide equilibration of **6** and without purification of **7a** gave, after chromatography, crystalline **7c** in an overall yield of 44%. Alternatively, pure **7a** was converted to the 6-*O*-tosyl derivative (**7b**) and then treated with sodium iodide in dimethylformamide giving readily crystalline **7c** in overall yield of 59% from **6**. A similar sequence using the crude acetonide equilibration mixture led to **7c** in 57% yield from **6**. Finally, the best overall conversion of **6** to **7c** involved iodination of the crude acid equilibrated mixture, containing principally **7a**, with triphenylphosphine and iodine,[28] a reaction giving crystalline **7c** in 67% yield



without any need for chromatography. Thus the key intermediate (**7c**) was obtained in an overall yield of 20% from fructose and is, hence, readily available.

Hydrolysis of the isopropylidene functions from **7a** was readily accomplished using an acidic ion exchange resin giving crystalline 6-deoxy-6-iodo-D-psicofuranose (**8a**) in 74% yield. This compound exhibited a sharp melting point but its NMR spectrum in Me_2SO-d_6–D_2O did not permit an assignment of anomeric configuration. Since the intermediates **4**–**7c** all showed significant negative rotations while **8a** had $[\alpha]^{23}D$ 14.6°, it is tempting to suggest that **8a** is, in fact, the α anomer. It is interesting to note that we were unable to observe any mutarotation in water, or in a mixture of water and pyridine. Benzoylation of **8a** readily gave the tetrabenzoate **8b** in 82% yield as a roughly 2:1 mixture of anomers as judged by ^1H NMR analysis. This mixture could not be further resolved by chromatography on silicic acid and attempts to isolate a single anomer by crystallization were unsuccessful. On the other hand, the tetra-*O*-*p*-nitrobenzoyl derivative **8c** could be resolved into its anomers by chromatography and the major isomer was isolated in crystalline form in 59% yield.

Since the anomeric configuration of **8** was not significant for further work, the readily available mixed benzoates (**8b**) were converted to 1,3,4-tri-*O*-benzoyl-6-deoxy-6-iodo-D-psicofuranosyl bromide (**9**) by reaction with anhydrous hydrogen bromide in methylene chloride. Without any attempt at purification, **9** was condensed with several different adenine derivatives. Firstly, N^6-hexanoyladenine[29] was treated with **9** in the presence of stannic chloride and an excess of mercuric cyanide, a mixture that was previously found to be effective as part of another project.[30] The use of N^6-octanoyladenine in order to increase the solubility of adenine has previously been reported.[31] By chromatography on silicic acid N^6-hexanoyl-9-(1,3,4-tri-*O*-benzoyl-6-deoxy-6-iodo-β-D-psicofuranosyl)adenine (**11a**) and its α anomer (**12a**) were isolated in yields of 46 and 12%, respectively. It should be noted that condensations of perbenzoylated hexulofuranosyl bromides could, in principle, condense to give either α or β nucleosides

Table I. 100-MHz NMR Chemical Shifts (ppm)

Cpd	Solvent[a]	C_1 H_a	C_1 H_b	C_3 H	C_4 H	C_5 H	C_6 H_a	C_6 H_b	Other
1	P/D_2O	4.85 (d)	5.06 (d)	5.71 (d)	4.94 (m)		4.71 (dd)	4.82 (dd)	8.42, 8.44 (s, 1, C_2 H, C_8 H)
2a[b]	C	6.52 (d, C_1, H)		6.40 (dd)	6.11 (dd)	4.60 (dt)	3.62 (d)		8.30, 8.57 (s, 1, C_2 H, C_8 H), 7.1–8.1 (m, 35, Ar)
2b[b]	P	7.07 (d, C_1, H)		6.77 (dd)	6.48 (dd)	4.80 (dt)	4.30 (d)		8.78, 9.42 (s, 1, C_2 H, C_8 H), 7.3, 8.0 (m, 20, Ar)
2c[b]	C	6.48 (d, C_1, H)		6.29 (dd)	5.94 (dd)	4.54 (dt)	3.67 (d)		8.43, 8.70 (s, 1, C_2 H, C_8 H), 7.4, 7.9 (m, 20, Ar)
3[b]	D	6.17 (d)		4.85 (ddd)	4.73 (br dd)		4.21 (d)	4.32 (br d)	8.17, 8.38 (s, 1, C_2 H, C_8 H), 5.52, 5.56 (d, 1, OH), 7.32 (s, 2, NH_2)
4	C	3.98 (d)	4.21 (d)	3.68 (br d)	4.10 (m)	4.10 (m)	4.00 (m)	4.17 (m)	1.36, 1.44, 1.51, 1.52 (s, 3, CMe_2)
5	C	3.96 (d)	4.60 (d)		4.72 (d)	4.5 (m)	4.08 (dd)	4.40 (dd)	1.39 (s, 6), 1.44, 1.53 (s, 3, CMe_2)
6	C	4.01 (d)	4.25 (d)	3.73 (dd)	4.42 (dd)	~4 (m)	~4 (m)	~4 (m)	1.37, 1.41, 1.49, 1.54 (s, 3, CMe_2), 2.34 (d, 1, C_3OH)
7a	C	4.02 (d)	4.31 (d)	4.61 (d)	4.88 (dd)	4.25 (m)	5.05 (dd)	5.22 (dd)	1.31, 1.39, 1.43, 1.49 (s, 3, CMe_2)
7b	C	3.98 (d)	4.25 (d)	4.53 (d)	4.67 (d)	3.9–4.3 (m)	3.9–4.3 (m)		1.28, 1.36 (6 H), 1.39 (s, 3, CMe_2), 2.44 (ArMe), 7.31, 7.78 (m, 4, Ar)
7c	P	4.21 (d)	4.46 (d)	4.74 (d)	4.93 (dd)	4.55 (m)	3.49 (ABX)		1.31, 1.45 (6 H), 1.56 (s, 3, CMe_2)
8b[c]	C	4.53 (d)	4.67 (d)	5.71 (d)	5.50 (dd)	4.44 (dd)	3.50 (ABX)		7.2–8.1 (m, 20, Ar)
8b[d]	C	4.50 (d)	4.81 (d)	5.90 (d)	5.77 (dd)	4.5 (m)	3.50 (ABX)		7.2–8.1 (m, 20, Ar)
8c	C	4.98 (d)	5.43 (d)	6.36 (d)	5.92 (dd)	4.70 (ddd)	3.55 (d)		7.9–8.3 (m, 16, Ar)
11a	C	5.13 (d)	5.39 (d)	6.94 (d)	5.68 (dd)	4.73 (ddd)	3.51 (dd)	3.63 (dd)	8.55, 8.63 (s, 1, C_2 H, C_8 H), 0.8–1.9 (m, 9, Aliph), 2.90 (t, 2, $COCH_2$), 7.2–8.1 m, 15, Ar)
11b	C	5.17 (d)	5.44 (d)	6.97 (d)	5.70 (dd)	4.72 (ddd)	3.54 (dd)	3.66 (dd)	8.63 (s, 2, C_2 H, C_8 H), 7.2–8.1 (m, 20, Ar), 9.27 (s, 1, NH)
11c	C	5.10 (d)	5.35 (d)	7.01 (d)	5.69 (dd)	4.70 (ddd)	3.49 (dd)	3.62 (dd)	8.19, 8.37 (s, 1, C_2 H, C_8 H)
12a	C	5.17 (d)	5.35 (d)	6.51 (d)	5.85 (dd)	4.82 (ddd)	3.43 (dd)	3.54 (dd)	8.19, 8.55 (s, 1, C_2 H, C_8 H), 0.8–1.9 (m, 9, aliph), 2.83 (t, 2, $COCH_2$), 9.05 (s, 1, NH)
12c	C	5.12 (d)	5.32 (d)	6.49 (d)	5.83 (dd)	4.74 (ddd)	3.42 (dd)	3.54 (dd)	7.85, 8.28 (s, 1, C_2 H, C_8 H), 7.1–8.15 (m, 15, Ar), 5.68 (s, 2, NH_2)
13	P/D_2O	4.50 (d)	4.98 (d)	5.24 (d)	5.47 (m)		4.67 (dd)	4.80 (dd)	8.50, 8.59 (s, 1, C_2 H, C_8 H)
14	P/D_2O	3.72 (d)	5.13 (d)	5.19 (d)	4.83 (d)	4.69 (br s)	3.84 (br s)		8.36, 8.50 (s, 1, C_2 H, C_8 H)
15a	C	4.98 (d)	5.28 (d)	6.10 (d)	5.65 (dd)	4.57 (ddd)	3.37 (dd)	3.54 (dd)	5.95 (d, 1, C_5 H), 7.94 (d, 1, C_6 H), 7.1–8.0 (m, 15, Ar)
15b	C	5.06 (d)	5.36 (d)	6.50 (d)	5.62 (dd)	4.58 (ddd)	3.37 (dd)	3.55 (dd)	2.21 (s, 3, NAc), 8.35 (d, 1, C_6 H), 7.2–8.1 (m, 16, Ar and C_5H)
16	P/D_2O	4.67 (d)	5.22 (d)	5.54 (d)	4.8 (m)		4.64 (dd)	4.77 (dd)	6.02 (C_5 H), 7.83 (C_6 H), 3.58 (s, 1.5, MeOH)
17	C	7.57 (d)		6.74 (dd)	5.50 (dd)	4.55 (m)	3.41 (dd)	3.55 (dd)	7.1–8.0 (m, 15, Ar)
18a	C	4.84 (d)	5.37 (d)	6.46 (d)	5.65 (dd)	4.65 (ddd)	3.47 (dd)	3.59 (dd)	3.96 (s, 3, OMe), 8.75 (s, 1, C_5 H), 7.2–8.05 (m, 15, Ar)
18b	C	4.85 (d)	5.39 (d)	6.40 (d)	5.80 (dd)	4.89 (m)	3.79 (dd)	3.98 (dd)	3.95 (s, 3, OMe), 8.70 (s, 1, C_5 H), 7.2–8.05 (m, 15, Ar)
18c	C	4.80 (d)	5.30 (d)	6.52 (d)	5.74 (dd)	4.8 (m)	4.31 (dd)	4.47 (dd)	1.96 (s, 3, OAc), 3.95 (s, 3, OMe), 8.64 (s, 1, C_5 H), 7.1–8.1 (m, 15, Ar)
19	C	4.94 (d)	5.67 (d)	7.14 (d)	5.53 (dd)	4.68 (ddd)	3.23 (dd)	3.44 (dd)	4.04 (s, 3, OMe), 7.97 (s, 1, C_5 H), 7.1–8.05 (m, 15, Ar)
20	C	4.88 (d)	5.25 (d)	6.52 (d)	6.13 (ddd)		4.56 (dd)	4.90 (dd)	3.95 (s, 3, OMe), 8.56 (s, 1, C_5 H), 7.1–8.0 (m, 15, Ar)
21	P/D_2O	4.84 (s)		5.40 (d)	5.17 (ddd)		4.66 (dd)	4.78 (dd)	9.10 (s, 1, C_5 H)
22	P/D_2O	4.79 (br s)		5.32 (d)	4.79 (m)	4.79 (m)	4.10 (dd)	4.32 (dd)	9.41 (s, 1, C_5 H)
23	C	4.06 (d)	4.31 (d)	4.66 (d)	4.83 (d)	4.42 (m)	4.42 (m)	4.42 (m)	1.35 (s, 6, CMe_2), 1.43, 1.46 (s, 3, CMe_2), 7.45 (m, 3, Ar), 8.05 (dd, 2, Ar)
24b[c]	C	4.90 (d)	5.34 (d)	6.31 (d)	6.06 (dd)	4.85 (m)	4.60 (dd)	4.85 (m)	6.9–8.5 (m, 25, Ar)
25a	C	5.01 (d)	5.29 (d)	6.63 (d)	5.82 (dd)	4.8 (m)	4.47 (dd)	4.73 (dd)	5.71 (d, 1, C_5 H), 7.1–8.1 (m, 2, Ar and C_6 H)
25b	P/D_2O	3.75–4.1 (m)		4.50 (d)	3.4 (m)	3.9 (m)	3.3–3.6 (m)		5.63 (d, 1, C_5 H), 7.90 (d, 1, C_6 H)

[a] Solvents are designated as C ($CDCl_3$), P (pyridine-d_5), D (Me_2SO-d_6). [b] Compounds **2** and **3** are numbered as though they were β-D-psicofuranosides. Thus the normal $C_{2'}$, $C_{3'}$, $c_{4'}$, $C_{5'a}$ and $C_{5'b}$ protons are referred to in this table as $C_{3'}$ H, $C_{4'}$ H, $C_{5'}$ H, $C_{6'a}$ H and $C_{6'b}$ H, respectively. [c] Major isomer. [d] Minor isomer.

Table II. First-Order Coupling Constants (Hz)

Compd	$J_{1a,1b}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$	Other
1	12	4.5				1.5	$J_{4,6a} = 1.5, J_{4,6b} \sim 0.5$
2a	$J_{1',2'} = 5.5$	5.5	4	4	4	0	
2b	$J_{1',2'} = 6$	6	3	3	3	0	
2c	$J_{1',2'} = 5.5$	5.5	5	5	5	0	
3	$J_{1',2'} = 5$	5				2	$J_{3',5'} \sim 0.5, J_{H,OH} = 5$
4	9	*a*	*a*	*a*	*a*	12	$J_{H,OH} = 5$
5	10		5.5	1.5	2	15	
6	9	4	6.5	*a*	*a*	*a*	$J_{H,OH} = 6.5$
7a	10	6	1	3.5	2.5	12.5	
7b	10	6	0	*a*	*a*	*a*	
7c	10	6	1	*a*	*a*	*a*	
8b[b]	12	6.5	3.5	4	4	*a*	
8b[c]	11.5	4.5	6.0	*a*	*a*	*a*	
8c	12	5	7	5	5	0	
11a	12	5.5	5.5	5	5	12	
11b	12	6	6	4	4	12	
11c	12	5.5	5.5	5	5	12	
12a	12	5	5	5	5	12	
12c	12	5.5	5.5	5	5	12	
13	12	5				1.5	$J_{4,6a} = 1.5, J_{4,6b} \sim 0.5$
14	10.5	6	0	~1	~1	0	
15a	12	6	6	5	5	12	$J_{5,6(\text{pyrimidine})} = 7.5$
15b	12	6	6	5	5	11	$J_{5,6(\text{pyrimidine})} = 7.5$
16	11.5	5				2	$J_{4,6a} = 1.5, J_{4,6b} = (a)$
17		6	7	5.5	5	11	$J_{1,3} = 1.5$
18a	12	5.5	5	5	5	13	
18b	12	5.5	5.5	3	*a*	12	
18c	11.5	5	6	4	3	12	
19	12	5	7	6	5	11	
20	12	5.5				3	$J_{4,6a} = 1.5, J_{4,6b} = 1.5$
21	0	5				2	$J_{4,6a} = 2, J_{4,6b} = 2$
22	*a*	4	*a*	3	2	12	
23	10	5.5	0	*a*	*a*	*a*	
24b[b]	11.5	4.5	7	3	*a*	11	
25a	12	5.5	5.5	3.5	3	12	$J_{5,6(\text{pyrimidine})} = 7.5$
25b	*a*	4.5	*a*	*a*	*a*	*a*	$J_{5,6(\text{pyrimidine})} = 7.5$

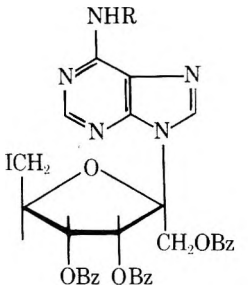
[a] Unresolved. [b] Major isomer. [c] Minor isomer.

since the relative degree of anchiomeric participation by the 1-*O*-benzoyl and 3-*O*-benzoyl groups is uncertain. In such furanose systems it has been found that the major product is, in fact, the anomer with a trans disposition to the 3-*O*-benzoate, indicating the predominant formation of a 2,3-*O*-benzoxoninium ion.[32] The absence of an anomeric proton in the resulting nucleosides makes the definitive assignment of configuration rather difficult and an examination of the ^{1}H NMR spectra of **11a** and **12a** (see Tables I and II) shows that the only significant differences lie in the chemical shifts of $C_{3'}$H and of one of the adenine ring protons. Unequivocal assignment of stereochemistry is, however, possible from subsequent transformations described below. It is interesting to note that the patterns for the benzoyl protons in **11a** and **12a** also differ markedly. Thus, in the major, β isomer (**11a**) the 15 aromatic protons appear as two groups of multiplets, the nine meta and para protons at 7.2–7.65 ppm and the six ortho protons at 7.7–8.1 ppm. In the α anomer (**12a**), however, 13 protons appear in the 7.0–7.65-ppm range and only two appear as a clean doublet of doublets ($J_{ortho} = 7.5$, $J_{meta} = 1.5$ Hz) at 8.04 ppm. Clearly, a single benzoyl group exists in an environment distinctly different from the other two, a situation that is compatible with the $C_{1'}$-*O*-benzoyl in the α anomer (**12a**). Alternatively, **9** was condensed with N^6-benzoylchloromercuriadenine[33] and, following chromatography on silicic acid, the β-psicofuranosyl derivative (**11b**) was isolated in 49% yield. The α nucleoside **12b** was not isolated. In this case the β configuration was apparent both from the conversion of **11b** to angustmycin A and from its NMR spectrum, the sugar portion of which was essentially identical with that of **11a**. The condensation of **9** with unsilylated adenine in the presence of stannic chloride and mercuric cyanide in acetonitrile was less efficient and led to the isolation of the β (**11c**) and α (**12c**) nucleosides in yields of 21 and 7%, respectively. In this reaction the adenine dissolved instantly upon addition of the stannic chloride, and while the yields are somewhat low, the direct formation of the *N*-glycoside from unprotected adenine is noteworthy. Once again, a 0.5-ppm downfield shift of the $C_{3'}$ proton in the β isomer and the presence of only two downfield benzoyl protons in the α anomer (**12c**) were the only significant differences in the NMR spectra of **11c** and **12c**. Presumably this consistent chemical shift difference for $C_{3'}$H is the consequence of not readily predictable differences in the anisotropic effects of the adjacent adenine or benzoyloxymethyl substituents. Some analogy for the effects of the heterocyclic ring on the chemical shift of $C_{4'}$H comes from an examination of the NMR spectra of the α and β anomers of N^6,$O^{2'}$,$O^{3'}$,$O^{5'}$-tetrabenzoyladenosine.[34] In the β-adenosine derivative $C_{1'}$ H and $C_{2'}$ H appeared at 5.92 ($J_{1',2'} = 4.5$ Hz) and 5.80 ppm ($J_{2',3'} = 5.5$ Hz), respectively, while the α anomer showed these protons at 6.42 ($J_{1',2'} = 5.5$ Hz) and 5.64 ppm ($J_{2',3'} = 5.5$ Hz). The deshielding of $C_{1'}$ H in the α anomer is well known[35] and, while the deshielding of $C_{2'}$ H (equivalent to $C_{3'}$ H in **11**) in the β anomer is smaller than that shown upon comparison of **11** and **12**, the shift is in the same direction.

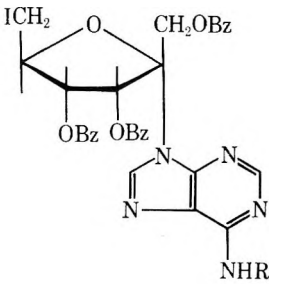
The dehydrohalogenation of **11** and **12** was first investigated using DBN. Treatment of **11b** with DBN in benzene under reflux for 45 min readily gave an olefin as shown by a positive test with dilute potassium permanganate spray on TLC plates. Following debenzoylation with methanolic ammonium hy-

droxide and chromatography on a column of Bio-Rad AG1 (X2) resin in the hydroxide form,[18] crystalline 9-(6-deoxy-β-D-*erythro*-hex-5-enofuran-2-ulosyl)adenine (**1**) was isolated in 48% yield as the hemimethanolate that had an identical melting point, mixture melting point, NMR spectrum, chromatographic mobility, and antimicrobial activity[4] with an authentic sample of decoyinine (angustmycin A) obtained through the courtesy of the Upjohn Co. Similar treatment of the α anomer **19a** with DBN in dimethylformamide at room temperature gave crystalline 9-(6-deoxy-α-D-*erythro*-hex-5-enofuran-2-ulosyl)adenine (**13**), the α anomer of angustmycin A, in 64% yield. The structure of **13** was apparent from its NMR spectrum (see Tables I and II), which was similar to that of **1** and clearly showed the presence of the 5′,6′ olefin.

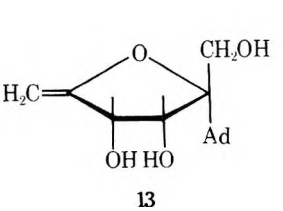
Alternatively, dehydrohalogenation and deacylation of **11a** could be efficiently achieved through treatment with methanolic sodium methoxide. In this case the product was purified by chromatography on silicic acid followed by crystallization from methanol giving pure **1** in 60% yield. It is interesting to note than an analytical sample crystallized from water was obtained in a nonsolvated form with mp 183.5–185 °C. Most previous reports on this substance have led to solvates, although nonsolvated decoyinine with mp 183–186 °C has been described in the patent literature.[36] Similar treatment of the α anomer **12a** with sodium methoxide led to the formation of two major products, the more abundant one of which did not contain an olefin as demonstrated by a negative test with permanganate spray. By chromatography on silicic acid these two substances were isolated in pure form. The minor component, isolated in crystalline form in only 13% yield, was identical with the α-angustmycin A (**13**) described above. The major crystalline component, isolated in 38% yield, was shown to have the same empirical formula as **13** but its NMR spectrum clearly confirmed that it was not an olefin. It did, however, give a positive test with the periodate–benzidine spray,[37] indicating the presence of a vicinal diol. While the NMR spectrum of this compound showed the usual magnetic nonequivalence of the $C_{1'}$ protons, the $C_{6'}$ protons were equivalent and appeared as a slightly broadened two-proton singlet (half-band width 3 Hz) at 3.84 ppm indicating very small coupling to $C_{5'}$ H ($J_{5',6'} \sim 1$ Hz) and a conformation rather different from other compounds in this series. The chemical shift of $C_{6'}$ H_2 suggests the presence of an oxygen substituent and this compound is considered to be 9-(1,6-anhydro-α-D-psicofuranosyl)adenine (**14**) arising from intramolecular displacement of the 6′-iodo function by the $C_{1'}$ oxygen anion. The formation of this substance provides unequivocal confirmation of the α configuration for **12a**.



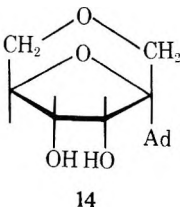
11a, R = $CO(CH_2)_4CH_3$
b, R = Bz
c, R = H



12a, R = $CO(CH_2)_4CH_3$
b, R = Bz
c, R = H



13



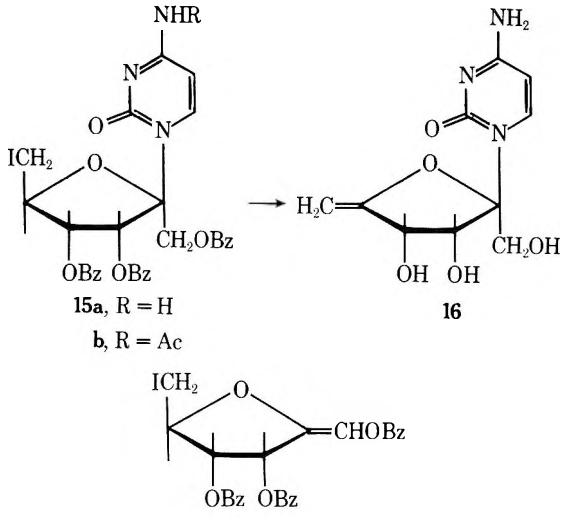
14

The successful synthesis of angustmycin A described above prompted us to also prepare several base analogues. The condensation of **9** with bis(trimethylsilyl)cytosine[38] in benzene in the presence of both stannic chloride and mercuric cyanide gave a crystalline nucleoside considered to be 1-(1,3,4-tri-*O*-benzoyl-6-deoxy-6-iodo-β-D-psicofuranosyl)cytosine (**15a**) in 56% yield. This method of condensation is a hybrid of the well-known methods of Wittenburg[39] and of Niedballa and Vorbrüggen.[40] In the absence of stannic chloride the yield of **15a** fell to 17–31% under various conditions and several byproducts were formed. One of these was isolated in low yield by chromatography on silicic acid and proved to be 2,5-anhydro-1,3,5-tri-*O*-benzoyl-2,6-dideoxy-6-iodo-D-*ribo*-hex-1-enitol (**17**). We have not found any close precedent for the formation of such an exocyclic glycal derived from a ketosyl halide. Its structure, however, appears on safe ground from its NMR spectrum, which retains the typical ABX pattern for the iodomethyl group but lacks that of the C_1-*O*-benzoyl function found in other members of this series. In its place one finds only a single, isolated vinyl proton at 7.57 ppm, a position quite compatible with what would be expected for such a substituted enol benzoate. A considerably less efficient condensation between N^4-acetylbis(trimethylsilyl)cytosine[39] and **9** occurred in the presence of mercuric cyanide, **15b** being isolated as a foam in only 20% yield.

Dehydrohalogenation of **15a** and **15b** was achieved using both sodium methoxide and DBN in dimethylformamide. The former method proved to be more efficient and crystalline 1-(6-deoxy-β-D-*erythro*-hex-5-enofuran-2-ulosyl)cytosine (**16**), the cytosine analogue of angustmycin A, was obtained in 84% yield. It should be noted that with possession of only a single anomer of **15a,b** the assignment of anomeric configuration is not without difficulty. The chemical shift of $C_{3'}$ H, which was distinctly different in the two adenine anomers, does not appear to provide an unequivocal answer when applied to the cytosine derivatives **15a** and **15b**. The $C_{3'}$ protons in **15a** and **15b** appeared at 6.10 and 6.50 ppm, respectively, these positions being closer to those in the α-adenine derivatives (**12a,b**) than to the desired β anomers. An examination of the NMR spectra of a considerable number of acylated adenine and cytosine nucleosides available in these laboratories shows that $C_{2'}$ H (corresponding to $C_{3'}$ H in the psicofuranosyl derivatives) in the cytosine compounds consistently appears at higher field (~5.4–5.7 ppm for 2′-*O*-acetates and ~5.7–5.9 ppm for 2′-*O*-benzoates) in the cytidine series than in the adenosine counterparts (~5.9–6.1 ppm for acetates and 6.2–6.4 ppm for benzoates). This effect, which is presumably due to the proximity of the C^2 carbonyl group in the pyrimidine ring, makes it difficult to draw any firm conclusions with only a single cytosine anomer available. Also, the NMR spectrum of 2′,3′,5′-tri-*O*-benzoyluridine[41b] was compared with that of its α anomer.[41a] In the β isomer $C_{1'}$ H and $C_{2'}$ H appeared at 6.31 and 5.75 ppm, respectively, while in the α isomer these protons were at 6.61 and 6.11 ppm. Once again, the deshielding of $C_{1'}$ H in the α anomer was expected,[35] but, unlike the adenosine analogues mentioned earlier, $C_{2'}$ H also appeared further downfield in the β isomer. Hence the observed chemical shift of $C_{3'}$ H in the pyrimidine derivatives (**15**) is not unexpected.

Several other, indirect arguments strongly point to the desired β configuration for the cytosine nucleosides. Firstly, it has been established that the condensation of acylated psicofuranosyl bromides with trimethylsilylpyrimidines leads exclusively to β nucleosides[9c] and the presence of the 6-iodo function in **9** would not be expected to greatly change this tendency. Secondly, treatment of **15a** with sodium methoxide gave the crystalline olefin **16** in 84% yield while similar

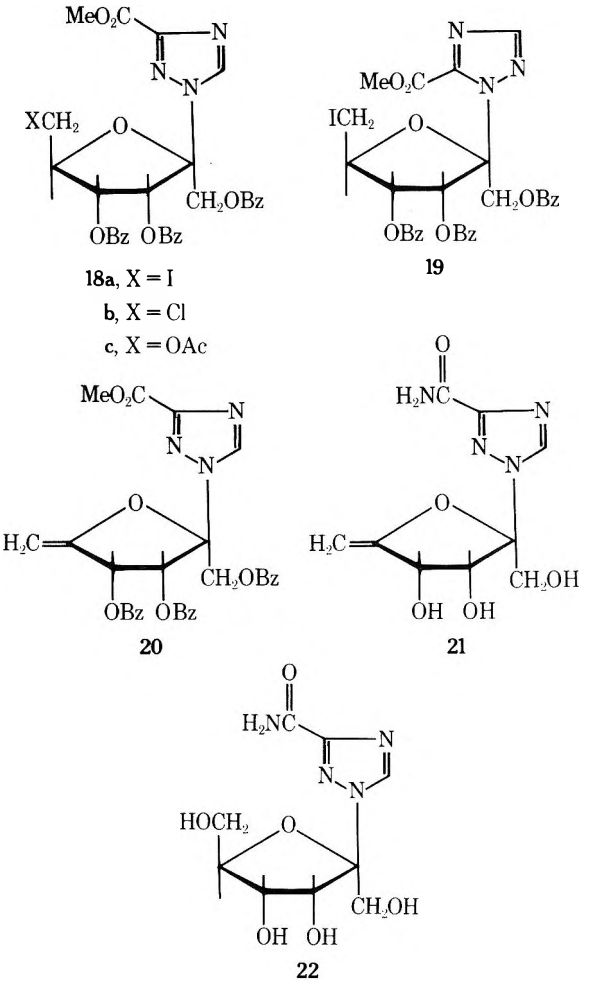
treatment of the α anomer (**12a**) in the adenine series led predominantly to the 1,6-oxide (**14**). If **15a** had, in fact, the α configuration one would expect the formation of an appreciable amount of a similar anhydro compound, which was not the case. Thirdly, it was hoped that the 5′,6′-olefin function would not play an overriding role in determination of the nature of the ORD spectra of these compounds. If this were the case, then the sign of the Cotton effect would provide direct evidence as to the anomeric configuration.[42] Unfortunately neither **1** nor **13**, the only anomeric pair of exocyclic olefins of value to us, gave well-defined ORD spectra, the intensities being very low. This effect has previously been noted for **1** and **3**.[43] Thus, while the effect of the 4′,5′ olefin is not readily predictable, the well-defined positive Cotton effect shown by **16** and similar to those of cytidine[42] and 1-(β-D-psicofuranosyl)cytosine[9c] offers further tentative support for the assigned β configuration. Various attempts to convert **15a** into the known 1-(β-D-psicofuranosyl)cytosine via displacement of the 6′-iodo function with silver acetate in aqueous acetic acid, with tetramethylammonium acetate in benzene, or with lithium benzoate in hexamethylphosphoramide gave an olefinic product, presumably the tribenzoate of **16**, as the only identifiable new product. This same olefin was also obtained upon attempted conversion of **15a** into an O^2,5′-cyclonucleoside by treatment with 1,5-diazabicyclo[5.4.0]undec-5-ene in methylene chloride.[44]



In view of the interesting antiviral properties exhibited by 1-(β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide,[45] we have also decided to prepare several related psicosyl derivatives. Thus *N*-trimethylsilyl-3-methoxycarbonyl-1,2,4-triazole[45] and **9** were condensed in benzene in the presence of mercuric cyanide at 60 °C. Following chromatography of the products on a column of silicic acid one major and several minor products were isolated as foams that failed to crystallize. The major product, isolated in 49–51% yields, was expected to be the 1-(1,3,4-tri-*O*-benzoyl-6-deoxy-6-iodo-β-D-psicofuranosyl)-3-methoxycarbonyl-1,2,4-triazole (**18a**) on the basis of the known preferential glycosidation of the nitrogen distal to the ester function in this triazole,[45,46] and the previously discussed predominant formation of β nucleosides from compounds related to **9**. ^{1}H NMR spectroscopy has recently been shown to provide a facile method for determination of the site of glycosidation in nucleosides derived from 3-methoxycarbonyl-1,2,4-triazole and related compounds.[46] The single triazole proton in the major product from the above reaction appeared at 9.15 ppm in Me_2SO-d_6, a position that assures the site of glycosidation as indicated for **18a**.[46]

Two other products were also isolated from the above reaction. The major of these, isolated as a foam in 19% yield, was isomeric with **18a** and was somewhat less polar. In contrast with **18a**, the NMR spectrum of this substance showed the single triazole proton as a singlet at 8.29 ppm in Me_2SO-d_6, allowing its assignment as the 1-glycosyl-5-methoxycarbonyl-1,2,4-triazole (**19**). There is no precedent for the formation of N^4-glycosyl derivatives from 3-methoxycarbonyl-1,2,4-triazoles. In another experiment, using a different preparation of **9** and giving **19** in 51% yield, a second byproduct was also isolated in 11% yield. The NMR spectrum of this substance was almost identical with that of **18a** except that the $C_{6'}$ protons were displaced 0.3–0.4 ppm downfield, and its mass spectrum clearly showed it to be the 6-chloro derivative **18b**. This compound must have arisen from some displacement of the iodo group during benzoylation of **8a** and points out that care must be taken in establishing the purity of **8b**. We have previously observed similar partial formation of chloro compounds during benzoylation of 5′-iodonucleosides.[47]

The treatment of **18a** with DBN in dimethylformamide at room temperature led to rapid dehydrohalogenation and crystalline 1-(1,3,4-tri-*O*-benzoyl-6-deoxy-β-D-*erythro*-hex-5-enofuran-2-ulosyl)-3-methoxycarbonyl-1,2,4-triazole (**20**) was isolated in 58% yield. The NMR spectrum of **20** showed the typical features shown by other furanose exocyclic vinyl ethers,[12] the $C_{6'}$ protons being nonequivalent and showing small geminal (J_{gem} = 3 Hz) and allylic ($J_{4',6'}$ = 1.5 Hz) couplings. Subsequent treatment of **20** with methanolic ammonium hydroxide gave the desired 1-(6-deoxy-β-D-*erythro*-hex-5-enofuran-2-ulosyl)-1,2,4-triazole-3-carboxamide (**21**) as an analytically pure foam in 85% yield. Once again the NMR spectrum of **21** showed C_5 H at 9.10 ppm in pyridine-d_5, this downfield position further supporting the

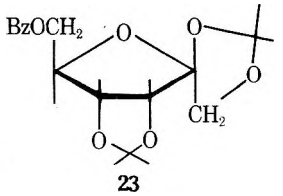


assigned site of glycosylation. It is interesting to note that, unlike the other compounds in this series, the $C_{1'}$ protons in **21** appear as a sharp singlet. It is not certain whether this is an indication of actual magnetic equivalence or the result of an AB pattern in which the central lines are adventitiously coincident and the outer lines vanishingly small.

While nucleophilic displacement of the 6-iodo function of **15a** with acetate anion was unsuccessful under a variety of conditions, the comparable displacement starting with **18a** could be achieved. Attempted displacements with lithium acetate or silver acetate in dimethylformamide under a variety of conditions led to fairly clean mixtures of the olefin **20** and the desired 6-*O*-acetyl derivative **18c** with the former usually predominating. Treatment of **18a** with 2 equiv of silver acetate in acetic acid–water (99:1) at 100 °C for 4.5 h, however, led predominantly to the desired acetate, which was isolated in 60% yield by chromatography. Surprisingly, in view of the acidic reaction conditions, the crystalline olefin **20** was also isolated in 5% yield. The structure of **18c** was obvious from its elemental analysis and NMR spectrum. Subsequent treatment of **18c** with methanolic ammonium hydroxide effected conversion to 1-(β-D-psicofuranosyl)-1,2,4-triazole-3-carboxamide (**22**) in 71% yield. The latter compound differs from the antiviral agent virazole (ribavarin)[45] only in the presence of an additional hydroxymethyl group at the anomeric center. This difference, however, is sufficient to render **22** biologically inactive with respect to antiviral, antibacterial, and antitumor activity.[48]

It was also of interest to consider the synthesis of some other β-D-psicofuranosyl nucleosides and the availability of **7a** would appear to provide a convenient intermediate for the preparation of the requisite 1,3,4,6-tetra-*O*-benzoyl-D-psicofuranosyl bromide (**24c**). Related psicofuranosyl halides have previously been prepared from psicose by different routes.[9] Our supply of **7a** was, however, exhausted and hence, in view of the successful nucleophilic displacement of the iodo function of **18a** by acetate, we considered a similar conversion of **8b** to the corresponding 6-*O*-acetyl derivative. This displacement was attempted under a number of conditions using silver acetate in acetic acid and when a reaction did occur, a plethora of unidentified products resulted. The use of tetrabutylammonium acetate in dimethylformamide was quite clean but the product was an olefin that was not further characterized. On the other hand, the 6-iodo diisopropylidene derivative (**7c**) reacted smoothly with lithium benzoate in dimethylformamide at 100 °C giving crystalline 6-*O*-benzoyl-1,2:3,4-di-*O*-isopropylidene-β-D-psicofuranose (**23**) in 90% yield. Acidic hydrolysis of the isopropylidene functions using a sulfonic acid ion exchange resin was essentially quantitative and the resulting anomeric mixture **24a** was benzoylated giving 1,2,3,4,6-penta-*O*-benzoyl-D-psicofuranose (**24b**). This too was a mixture of anomers with one component predominating. The NMR spectrum recorded in Tables I and II is that of the major anomer. Conversion of **24b** to the glycosyl bromide **24c** was achieved through treatment with hydrogen bromide in methylene chloride. Without purification the bromide was condensed with bis(trimethylsilyl)cytosine in the presence of mercuric cyanide giving homogeneous 1-(1,3,4,6-tetra-*O*-benzoyl-β-D-psicofuranosyl)cytosine (**25a**) in 33% yield. The same condensation could be more easily achieved using unsilylated cytosine, but in this case required stannic chloride and gave **25a** in an identical yield (33%). Debenzoylation of the latter compound then provided 1-(β-D-psicofuranosyl)cytosine (**25b**) as a crystalline dihydrate that lost water at 95–110 °C and then melted at 208–209 °C. The latter melting point and the ultraviolet spectrum of **25b** are identical with those reported for **25b** recently prepared via a different route.[9c] In view of the extensive studies of the Prague group on psicofuranosyl nucleosides[9c,d] we have not further extended this work.

It is clear from this paper that iodo sugars such as **9** provide versatile intermediates for the synthesis of angustmycin A and its base analogues. Subsequent papers will describe the synthesis of a number of other 4′,5′-unsaturated purine nucleosides,[49] some of which are useful starting materials for the synthesis of other natural products such as nucleocidin.[50]



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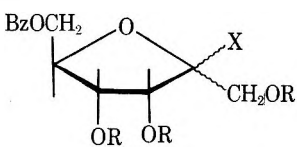
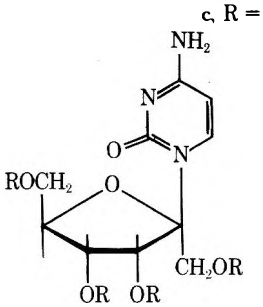


24a, R = H, X = OH
b, R = Bz, X = OBz
c, R = Bz, X = Br



25a, R = Bz
b, R = H

Experimental Section

General Methods. Proton magnetic resonance (NMR) spectra were obtained using a Varian HA-100 spectrometer and ^{13}C NMR spectra using a Bruker WH-90 spectrometer operating at 22.62 MHz. Spectra are recorded in parts per million downfield of an internal standard of tetramethylsilane. Gas–liquid chromatography was done using a Hewlett-Packard Model 402 instrument. Preparative thin layer chromatography and column chromatography were conducted on silica gel GF-254 from E. M. Laboratories, Elmsford, N.Y. Solutions were dried with $MgSO_4$ during workup. Melting points are corrected.

***N*⁶,*N*⁶,*O*²′,*O*³′-Tetrabenzoyladenosine (2b).** Benzoyl chloride (564 ml, 0.47 mol) was added dropwise to a stirred partial solution of 5′-*O*-trityladenosine (23.9 g, 47 mmol) in pyridine (300 ml) at 0 °C and the mixture was stored in the dark for 48 h. It was then added to ice water (4 l.) and extracted into chloroform. The organic phase was washed with aqueous sodium bicarbonate and water, dried, evaporated in vacuo, coevaporated with benzene, and then precipitated from chloroform with hexane giving 42.2 g (97%) of almost pure 5′-*O*-trityltetrabenzoyladenosine (**2a**):[14] λ_{max} (MeOH) 228 nm (ε 49 100), 272 (2700); $[\alpha]^{23}D$ −51.8° (*c* 0.5, $CHCl_3$); NMR (see Table I). This material (41.7 g, 45 mmol) was dissolved in a 0.56 M solution of hydrogen chloride in chloroform (230 ml) and stored at room temperature for 1 h. The solution was then evaporated and a solution of the residue in chloroform was washed with aqueous sodium bicarbonate and water, dried, and evaporated. Crystallization from chloroform–benzene gave 26.39 g (86%) of **2b** with mp 182–184 °C. An analytical sample had mp 183–185 °C (reported[14] mp 185 °C): λ_{max} (MeOH) 231 nm (ε 32 900), 273 (17 000); $[\alpha]^{23}D$ −20.3° (*c* 0.5, $CHCl_3$).

5′-Deoxy-5′-iodo-*N*⁶,*N*⁶,*O*²′,*O*³′-tetrabenzoyladenosine (2c). A solution of **2b** (3.41 g, 5 mmol) and methyltriphenoxyphosphonium iodide (3.35 g, 7.7 mmol)[16] in dimethylformamide (20 ml) was kept at 20 °C for 10 min. Following addition of methanol (0.5 ml), the solvent was evaporated and a chloroform solution of the residue was washed with aqueous sodium thiosulfate and water, dried, and evaporated. Crystallization from ethanol gave 3.40 g (87%) of **2c** with mp 188–189 °C: λ_{max} (MeOH) 231 nm (ε 43 800), 274 (22 800); $[\alpha]^{23}D$ −96.4° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{38}H_{28}N_5O_7I$ (793.55): C, 57.51; H, 3.55; I, 15.99. Found: C, 57.67; H, 3.78; I, 16.33.

9-(5-Deoxy-β-D-*erythro*-pent-4-enofuranosyl)adenine (3). A. Using Silver Fluoride. Finely powdered silver fluoride (130 mg, 1 mmol) was added under nitrogen to a solution of **2c** (794 mg, 1 mmol) in pyridine (10 ml) and stirred in the dark at room temperature

for 3 days. The mixture was then diluted with ethyl acetate (200 ml) and filtered. The filtrate was washed with aqueous sodium bicarbonate and water, dried, and evaporated, leaving a residue that was treated with methanol–concentrated ammonium hydroxide (1:1) at room temperature for 24 h and evaporated. The residue was coevaporated several times with ethanol and then applied in methanol–water (3:7) to a 1 × 15 cm column of Bio-Rad AG1 (X2) resin (OH^-).[18] The column was thoroughly washed with methanol–water (3:7) and then eluted with methanol–water (4.5:5.5) giving 5200 OD_{259} units (35%) of **3**. Crystallization from ethanol gave 36 mg (15%) of **3** with mp 185–186 °C (reported[13] mp 195 °C dec), λ_{max} (MeOH) 259 nm (ϵ 14 300).

Anal. Calcd for $C_{10}H_{11}N_5O_3$ (249.24): C, 48.19; H, 4.45; N, 28.10. Found: C, 48.38; H, 4.42; N, 27.94.

B. Using DBN. A solution of **2c** (0.79 g, 1 mmol) and 1,5-diazabicyclo[4.3.0]non-5-ene (0.25 g, 2 mmol) in dimethylformamide (50 ml) was kept at room temperature for 18 h and then evaporated to dryness. The residue was hydrolyzed with methanolic ammonium hydroxide and chromatographed as in A above giving 11 560 OD_{259} units (77%) of **3**. Crystallization from ethanol gave 179 mg (72%) of pure **3** with mp 185–186 °C and identical with that above.

1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranose (4). A suspension of fructose (1235 g, 6.86 mol) in a mixture of acetone (12 l.), 2,3-dimethoxypropane (500 ml), and 70% perchloric acid (1.2 ml) was stirred at room temperature for 70 h. Analysis by GLC (3% OV-225 at 130 °C) showed the presence of a 3:1 mixture of **4** and its 2,3:4,5-di-*O*-isopropylidene isomer. Concentrated ammonium hydroxide (1 ml) was added and the mixture was evaporated leaving a crystalline residue that was dried in vacuo overnight and then dissolved in chloroform (3 l.). The solution was washed three times with water (1 l.) and the aqueous extracts were back-extracted with chloroform. The dried chloroform phases were evaporated and crystallized from chloroform–hexane giving 686 g (38.5%) of **4** with mp 117.5–118 °C (reported[22] mp 119 °C) and showing a single peak by GLC analysis: ^{13}C NMR ($CDCl_3$) C_1 (72.43), C_2 (104.71), C_3 (70.48), C_4 (77.37), C_5 (73.47), C_6 (60.89), CMe_2 (26.01, 26.37, 26.50, 27.99), CMe_2 (109.52, 111.96).

1,2:4,5-Di-*O*-isopropylidene-β-D-*erythro*-2,3-hexodiulo-2,6-pyranose (5). A solution of anhydrous phosphoric acid in dimethyl sulfoxide (5 M, 85 ml, 0.42 mol) was added to a solution of **4** (232 g, 0.9 mol) and dicyclohexylcarbodiimide (557 g, 2.7 mol) in a mixture of dimethyl sulfoxide (340 ml), ethyl acetate (112 ml), and pyridine (68 ml). After 10 min an exothermic reaction commenced and the mixture was stirred in ice for 5 min and then at room temperature for 24 h. The mixture was then filtered and the dicyclohexylurea was washed with ethyl acetate (1.2 l.). A solution of oxalic acid dihydrate in methanol (8 M, 316 ml, 2.5 mol) was added gradually to the combined filtrates and after gas evolution had ceased the mixture was filtered and the dicyclohexylurea was washed with ethyl acetate. The filtrates were washed twice with saturated aqueous sodium chloride (500 ml) and then with aqueous sodium bicarbonate (2 × 500 ml) and water (2 × 250 ml). The organic phase was dried, evaporated, and crystallized from ethanol, giving 189 g of **5** in two crops. The final mother liquors were evaporated and a solution of the residue in ethyl acetate was washed with water, dried, evaporated, and crystallized from ethanol, giving a third crop (31 g) of **5**. GLC analysis of the first crop showed the presence of an impurity which was removed by recrystallization from ethanol (1.5 l.) giving 23 g of 1,3-dicyclohexylparabanic acid (**10**) with mp 175–176 °C (reported[26] mp 174–175 °C): λ_{max} (MeOH) 223 nm (ϵ 1500), 263 (sh, 500); NMR ($CDCl_3$) 1.0–2.2 ppm (m, 20 aliphatic), 4.0 (m, 2, NCH); mass spectrum (70 eV) *m/e* 278 (M^+), 197 (M^+ − cyclohexene), 115 (*m/e* 197 − cyclohexene), 83 ($C_6H_{11}^+$). The mother liquors after removal of **10** were evaporated and the residue combined with crops 2 and 3 from above. Crystallization from hexane (750 ml) gave 184 g (80%) of pure **5** with mp 101–102.5 °C (reported[23b] mp 101.5–102.5 °C). By further crystallization of the mother liquors from several experiments as above the total yield of pure **5** was raised to 85%: ^{13}C NMR ($CDCl_3$) C_1 (70.12), C_2 (104.29), C_3 (197.17), C_4 (76.01), C_5 (78.05), C_6 (60.24), CMe_2 (26.07, 26.07, 26.56, 27.17), CMe_2 (110.73, 113.95).

1,2:4,5-Di-*O*-isopropylidene-β-D-psicopyranose (6). A solution of sodium borohydride (21 g, 0.55 mol) in ethanol (300 ml) was added over 30 min to a stirred solution of **5** (173 g, 0.67 mol) ethanol (2.2 l.) at 0 °C. After a further 15 min the solvent was removed in vacuo, the residue was partitioned between ether (2.8 l.) and water, and the aqueous phase was back-extracted with ether. The combined ether phases were dried and evaporated leaving a crystalline residue that was washed with cold pentane giving 164 g (94%) of **6** with mp 62–63 °C (reported mp 62–64,[23c] 68–69 °C[23d]) that gave a single peak by GLC analysis (3.8% UC-W column at 140 °C): ^{13}C NMR ($CDCl_3$) C_1 (73.08), C_2 (105.10), C_3 (68.89), C_4 (72.33), C_5 (72.04), C_6 (61.34), CMe_2 (25.16, 26.07, 26.20, 26.56), CMe_2 (109.56, 111.18).

1,2:3,4-Di-*O*-isopropylidene-β-D-psicofuranose (7a). A solution of **6** (10.3 g, 39.6 mmol) in a mixture of acetone (90 ml) and 2,2-dimethoxypropane (10 ml) containing 70% perchloric acid (0.15 ml) was kept at room temperature for 17 h and then made basic with concentrated ammonium hydroxide (0.3 ml) and evaporated to dryness. The residue was dissolved in chloroform, washed with water, dried, evaporated, and distilled in a Kugelrohr apparatus[51] at 10^{-3} mm. Acetone polymers were first removed at 40–50 °C and then **7a** distilled at 70 °C giving 6.4 g (62%) of ~98% pure (GLC on OV-101 at 130 °C) crystalline product. Recrystallization from chloroform–hexane gave mp 56–56.5 °C, but only with considerable loss (reported[23b] mp 56–57.5 °C).

1,2:3,4-Di-*O*-isopropylidene-6-*O*-*p*-toluenesulfonyl-β-D-psicofuranose (7b). **A.** A solution of **7a** (1.80 g, 6.9 mmol) and *p*-toluenesulfonyl chloride (2.08 g, 10.9 mmol) in pyridine (30 ml) was kept at room temperature for 48 h, quenched with water, and evaporated to dryness. A solution of the residue in benzene was filtered and evaporated to dryness and the residue was crystallized from hexane giving 2.5 g (87%) of **7b** with mp 99.5–100 °C (reported[21b] mp 98–99 °C), $[\alpha]^{23}D$ −40.4° (c 1.0, $CHCl_3$).

B. A solution of **6** (40 g, 154 mmol) and concentrated sulfuric acid (2.4 ml) in acetone (1 l.) was kept at room temperature for 27 h and then made basic with concentrated ammonium hydroxide (10 ml), filtered, and evaporated to dryness. A solution of the residue in ether (600 ml) was washed with water (3 × 50 ml), dried, and evaporated. The residue was treated with *p*-toluenesulfonyl chloride (44.5 g, 232 mmol) in pyridine at room temperature for 24 h, worked up as in A, and crystallized from hexane giving 37.4 g (59% from **6**) of **7b** identical with that from A.

6-Deoxy-6-iodo-1,2:3,4-di-*O*-isopropylidene-β-D-psicofuranose (7c). **A.** A solution of **7b** (18.0 g, 43.5 mmol) and sodium iodide (20.0 g, 133 mmol) in dimethylformamide (250 ml) was heated at 110 °C for 2.5 h and then cooled. After evaporation of the solvent the residue was stirred with hexane (400 ml) and filtered, the precipitate being once more extracted with hexane (200 ml). Evaporation of the filtrates left 15.7 g (98%) of pure crystalline **7c**. An analytical sample from aqueous methanol had mp 44–44.5 °C; $[\alpha]^{23}D$ −74.3° (c 0.5, $CHCl_3$); ^{13}C NMR ($CDCl_3$) C_1 (69.83), C_2 (113.91), C_3 (85.63), C_4 (83.68), C_5 (86.25), C_6 (6.79), CMe_2 (26.59, 26.46, 26.46, 25.19), CMe_2 (113.00, 111.96).

Anal. Calcd for $C_{12}H_{19}O_5I$ (370.18): C, 38.93; H, 5.17. Found: C, 38.68; H, 5.09.

B. A solution of **7a** (7.8 g, 30 mmol) and methyltriphenoxyphosphonium iodide (16.3 g, 36 mmol) in a mixture of dimethylformamide (45 ml) and pyridine (5.8 ml) was kept at room temperature for 15 min. After addition of methanol (1 ml) the solvents were evaporated and a solution of the residue in chloroform was washed with aqueous sodium thiosulfate and water. The organic phase was evaporated and the residue was chromatographed on a column of alumina (450 g) (deactivated with 5% water) using benzene. Evaporation of the major product gave 6.30 g (57%) of crystalline **7c** that was homogeneous by GLC (3.8% UC-W at 160 °C) and identical with that from A.

C. The crude, undistilled product obtained by equilibration of pyranose **6** (10.3 g, 39.6 mmol) with perchloric acid as described for **7a** was treated with methyltriphenoxyphosphonium iodide (25 g, 55 mmol) and worked up as in B above. Following chromatography as above 6.38 g (44% from **6**) of crystalline **7c** was obtained.

D. A solution of **6** (225 g, 0.86 mol) in acetone (6.3 l.) was equilibrated and worked up as described in the preparation of **7a** giving 196 g of crude product. This was dissolved in a mixture of benzene (1.3 l.) and pyridine (75 ml) and to it was added triphenylphosphine (262 g, 1 mol) and iodine (254 g, 1 mol). After 11 h at room temperature, methanol (20 ml) was added, the mixture was filtered, and the precipitate was washed with benzene (1 l.). Following evaporation of the filtrates the residue was extracted four times with hexane (1 l.) and the combined extracts were washed with aqueous sodium thiosulfate and water. The aqueous phases were back-extracted with hexane and the combined hexane phases were dried and evaporated. Decolorization with charcoal and crystallization from aqueous methanol gave 215 g (67% from **6**) of **7c** identical with that above.

6-Deoxy-6-iodo-D-psicofuranose (8a). A suspension of **7c** (50 g, 135 mmol) and Bio-Rad AG 50W (H^+) resin (100 ml) in water (500 ml) was stirred at 60 °C for 4 h and then cooled and filtered. The filtrate was neutralized with barium carbonate and filtered at 5 °C, the precipitate being washed with acetone. The filtrates were evaporated and the residue was crystallized from acetone–chloroform giving 28.9 g (74%) of **8a** with mp 80.5–81 °C; $[\alpha]^{23}D$ 14.6° (c 1.0, H_2O) with no observed mutarotation.

Anal. Calcd for $C_6H_{11}O_5I$ (290.05): C, 24.84; H, 3.82. Found: C, 24.58; H, 3.71.

1,2,3,4-Tetra-*O*-benzoyl-6-deoxy-6-iodo-D-psicofuranose (8b). Benzoyl chloride (21 ml, 180 mmol) was added over 30 min to a stirred solution of **8a** (8.7 g, 30 mmol) in pyridine (150 ml) at 0 °C. After a further 24 h at room temperature, methanol (20 ml) was added and the mixture was evaporated. A solution of the residue in chloroform was washed with water, dried, and evaporated, leaving an orange syrup (23.5 g). This was chromatographed on a column of silicic acid (500 g) using benzene and benzene containing 5% and 10% ethyl acetate giving 17.44 g (82%) of **8b** as a TLC homogeneous foam that was a roughly 2:1 mixture of anomers by NMR. An analytical sample was prepared by preparative TLC using benzene–ethyl acetate (19:1) but no separation of anomers was possible.

Anal. Calcd for $C_{34}H_{27}O_9I$ (706.48): C, 57.80; H, 3.85. Found: C, 58.03; H, 4.08.

1,2,3,4-Tetra-*O*-*p*-nitrobenzoyl-6-deoxy-6-iodo-D-psicofuranose (8c). The reaction of **8a** (1.0 g, 3.4 mmol) with *p*-nitrobenzoyl chloride (5.1 g, 27 mmol) in pyridine (60 ml) at 3 °C for 2 days was worked up as for **8b**. Chromatography on a column of silicic acid (200 g) using benzene–ethyl acetate (97:3) led to a separation of anomers, the major, less polar isomer being then crystallized from chloroform–hexane, giving 1.79 g (59%) of **8c** with mp 173–174 °C, λ_{max} (dioxane) 257 nm (ϵ 53 200).

Anal. Calcd for $C_{34}H_{23}IN_4O_{17}$ (886.45): C, 46.06; H, 2.61; N, 6.32. Found: C, 45.95; H, 2.52; N, 6.49.

A small amount (443 mg, 14%) of the more polar anomer was eluted but not explored further.

1,3,4-Tri-*O*-benzoyl-6-deoxy-6-iodo-D-psicofuranosyl Bromide (9). Anhydrous hydrogen bromide was slowly passed through a solution of **8b** (10.59 g, 15 mmol) in methylene chloride (40 ml) at 0 °C for 1.25 h. The mixture was then evaporated to dryness and the residue was coevaporated four times with a 3:1 mixture of toluene and dichloromethane (30 ml) and then once with benzene. The resulting viscous semicrystalline syrup was used directly for condensation reactions.

***N*⁶-Hexanoyl-9-(1,3,4-tri-*O*-benzoyl-6-deoxy-6-iodo-β-D-psicofuranosyl)adenine (11a) and Its α Anomer (12a).** Anhydrous stannic chloride (0.24 ml, 2 mmol) was added under nitrogen to a stirred solution of N^6-hexanoyladenine (350 mg, 1.5 mmol)[29] and mercuric cyanide (760 mg, 3 mmol) in acetonitrile. The mixture was stirred at 60 °C for 2 h and then evaporated leaving a residue that was dissolved in methylene chloride and filtered. The filtrate was washed with aqueous sodium bicarbonate, filtered through Celite, and further washed with 30% aqueous potassium iodide and then water. The organic phase was dried and evaporated leaving a yellow residue (780 mg) that was chromatographed on a column of silicic acid (70 g) using benzene–ethyl acetate (85:15) giving a clean separation of two anomeric products. Elution of the less polar, major isomer gave 373 mg (46%) of **11a** as a homogeneous foam: λ_{max} (MeOH) 231 nm (ϵ 43 000), 273 (23 100), 281 (17 200).

Anal. Calcd for $C_{38}H_{36}N_5O_8I$ (817.6): C, 55.82; H, 4.44; N, 8.57. Found: C, 55.94; H, 4.53; N, 8.42.

Continued elution with the same solvent gave 99 mg (12%) of the α anomer (**12a**) as a homogeneous white foam: λ_{max} (MeOH) 231 nm (ϵ 41 000), 273 (2000), 280 (sh, 15 700).

Anal. Calcd for $C_{38}H_{36}N_5O_8I$ (817.6): C, 55.82; H, 4.44; N, 8.57. Found: C, 55.65; H, 4.50; N, 8.60.

***N*⁶-Benzoyl-9-(1,3,4-tri-*O*-benzoyl-5-deoxy-5-iodo-β-D-psicofuranosyl)adenine (11b).** A suspension of N^6-benzoylchloromercuriadenine (1.42 g, 3 mmol)[33] and **9** (from 2.5 g, 3.5 mmol, of **8b** as above) in nitromethane was stirred at room temperature for 48 h and then evaporated to dryness. The residue was stirred with ethyl acetate and filtered, the filtrate then being washed with saturated aqueous sodium iodide and with water. The organic phase was dried, evaporated, and purified by preparative TLC on five plates using benzene–ethyl acetate (4:1). Elution of the major band gave 1.2 g (49%) of homogeneous (TLC, NMR) **11b** as a foam, $[\alpha]^{23}D$ −95.4° (c 0.14, $CHCl_3$).

Anal. Calcd for $C_{39}H_{30}N_5O_8I$ (823.58): C, 56.87; H, 3.67. Found: C, 56.60; H, 3.53.

9-(1,3,4-Tri-*O*-benzoyl-5-deoxy-5-iodo-β-D-psicofuranosyl)adenine (11c) and Its α Anomer (12c). Anhydrous stannic chloride (0.24 ml, 2 mmol) was added to a stirred mixture of adenine (200 mg, 1.5 mmol), **9** (from 1 mmol of **8b**), and mercuric cyanide (760 mg, 3 mmol) in acetonitrile (20 ml) at room temperature, leading to immediate dissolution of the adenine. The mixture was then heated at 60 °C for 2 h and evaporated. A suspension of the residue in chloroform was filtered and the filtrate was washed with aqueous sodium bicarbonate, 30% aqueous potassium iodide, and water. It was then dried and evaporated leaving a yellow residue (570 mg) that was chromatographed on a column of silicic acid (60 g) using carbon tetrachloride–acetone (7:3). Elution of the less polar product gave 154 mg (21%) of **11c** as a white foam: λ_{max} (MeOH, H^+) 231 nm (ϵ 42 200), 258 (18 000), 265 (16 500).

Anal. Calcd for $C_{32}H_{26}N_5O_7I$ (719.5): C, 53.42; H, 3.64; N, 9.73. Found: C, 53.60; H, 3.76; N, 9.51.

Continued elution gave 48 mg (7%) of **12c** contaminated with a trace of **11c**. Crystallization from chloroform–hexane gave pure **12c** with mp 192–193 °C: λ_{max} (MeOH, H^+) 232 nm (ϵ 45 100), 258 (17 100), 264 (16 200).

Anal. Calcd for $C_{32}H_{26}N_5O_7I$ (719.5): C, 53.42; H, 3.64; N, 9.73. Found: C, 53.59; H, 3.78; N, 9.78.

9-(6-Deoxy-β-D-*erythro*-hex-5-enofuran-2-ulosyl)adenine (1, Angustmycin A). A. A solution of **11a** (500 mg, 0.61 mmol) in 0.08 M methanolic sodium methoxide (38 ml) was heated under reflux for 3 h, then neutralized with glacial acetic acid and evaporated to dryness. The residue was partitioned between water and chloroform and the aqueous phase was evaporated leaving a reddish syrup (550 mg) that was dissolved in methanol (5 ml) containing silicic acid (2 g) and evaporated to dryness. The silica was then added to the top of a column of silicic acid (60 g) and the column was eluted with chloroform–methanol (85:15). Evaporation of the major peak followed by crystallization from methanol gave 102 mg (60%) of homogeneous (TLC and NMR) **1** with mp 178–180 °C. An analytical sample from water had mp 183.5–185 °C (reported multiple mp with final decomposition at 164.5–166.5[7] and 156–159 °C[13] for a hydrate and 183–186 °C for anhydrous[36]): $[\alpha]^{23}D$ 46.4° (c 0.46, H_2O); λ_{max} (MeOH, OH^-) 260 nm (ϵ 15 500).

Anal. Calcd for $C_{11}H_{13}N_5O_4$ (279.25): C, 47.31; H, 4.69; N, 25.08. Found: C, 47.43; H, 4.51; N, 25.24.

B. A solution of **11b** (820 mg, 1 mmol) and DBN (0.2 ml, 1.5 mmol) in benzene (20 ml) was heated under reflux for 45 min and then cooled and decanted from a brown gum. The supernatant was evaporated and the residue was treated with methanol (20 ml) and concentrated ammonium hydroxide (2 ml) for 24 h at room temperature. Following evaporation of the solvent a solution of the residue in methanol–water (3:7) was applied to a 1 × 15 cm column of Bio-Rad AG1 (X2) resin in the hydroxide form. The column was washed with methanol–water (3:7) and then eluted with methanol–water (1:1). Evaporation of the major peak followed by crystallization from methanol gave 142 mg (48%) of **1** as the hemimethanolate which softened at 133 °C and melted with decomposition at 170 °C. The melting point and mixture melting point were identical with those of an authentic sample of **1** obtained from the Upjohn Co. and the NMR spectra were also identical and identical with that from A above.

9-(6-Deoxy-α-D-*erythro*-hex-5-enofuran-2-ulosyl)adenine (13) and 9-(1,6-Anhydro-α-D-psicofuranosyl)adenine (14). A. A solution of **12a** (82 mg, 0.1 mmol) and DBN (0.04 ml, 0.3 mmol) in dimethylformamide (0.5 ml) was kept at room temperature for 24 h. Methanol (0.5 ml) was then added and the solution was stored for a further 54 h. The solution was evaporated and the residue was purified by preparative TLC using chloroform–methanol (85:15). Elution of the major band followed by crystallization from methanol gave 18 mg (64%) of **13** with mp 193–194.5 °C, λ_{max} (MeOH, OH^-) 259 nm (ϵ 13 700).

Anal. Calcd for $C_{11}H_{13}N_5O_4$ (279.25): C, 47.31; H, 4.69; N, 25.08. Found: C, 47.30; H, 5.04; N, 25.01.

B. A solution of **12a** (500 mg, 0.61 mmol) in 0.08 M methanolic sodium methoxide (38 ml) was heated under reflux for 8 h and then a further 2 mmol of sodium methoxide was added and heating was continued for 16 h. The cooled solution was neutralized with acetic acid and evaporated, and the residue was partitioned between chloroform and water. The aqueous phase was evaporated and the residue was adsorbed on silicic acid (3 g) and added to the top of a column of silicic acid (70 g). Elution with chloroform–methanol (9:1) gave a permanganate negative product that was crystallized from pyridine–ether giving 65 mg (38%) of **14** with mp 292–294 °C, λ_{max} (MeOH) 259 nm (ϵ 15 500).

Anal. Calcd for $C_{11}H_{13}N_5O_4$ (279.25): C, 47.31; H, 4.69; N, 25.08. Found: C, 47.44; H, 4.75; N, 25.04.

Continued elution with chloroform–methanol (85:15) gave 50 mg of crude **13** contaminated with some **14**. Further purification by preparative TLC using chloroform–methanol (4:1) followed by crystallization from methanol gave 23 mg (13%) of **13** identical with that from A above.

1-(1,3,4-Tri-*O*-benzoyl-6-deoxy-6-iodo-β-D-psicofuranosyl)cytosine (15a). A. A solution of sublimed bis(trimethylsilyl)cytosine (900 mg, 3.5 mmol),[38] **9** (from 2.1 g, 3 mmol, of **8b**), and stannic chloride (0.7 ml, 6 mmol) in benzene was stirred at 60 °C for 1.5 h in

the presence of finely powdered mercuric cyanide (2.3 g, 9 mmol). Following evaporation of the solvent the residue was suspended in chloroform and filtered. The filtrate was washed with saturated aqueous sodium bicarbonate, filtered, washed with 30% aqueous potassium iodide and with water, dried, and evaporated. The residue was chromatographed on a column of silicic acid (180 g) using chloroform–acetone (3:2). The major peak was evaporated giving 1.6 g (56%) of crystalline **15a** with mp 125–127 °C from chloroform–hexane. An analytical sample had mp 127–128 °C: λ_{max} (MeOH, H^+) 230 nm (ϵ 46 000), 276 (17 200), 281 (17 200).

Anal. Calcd for $C_{31}H_{26}N_3O_8I$ (695.45): C, 53.54; H, 3.77; N, 6.04. Found: C, 53.64; H, 3.64; N, 5.85.

B. In similar experiments using **9** (10 mmol), bis(trimethylsilyl)-cytosine (13 mmol), and mercuric cyanide (22 mmol) in benzene at 60 °C for 1.5 h in the absence of stannic chloride, the yield of crystalline **15a** was 31%, while after 24 h at room temperature **15a** was obtained in 25% yield. In these cases several less polar minor byproducts were also formed and one of these was isolated during chromatography giving 116 mg (2%) of **17** with mp 121.5–122 °C: λ_{max} (MeOH) 230 nm (ϵ 42 700), 260 (sh, 1900).

Anal. Calcd for $C_{27}H_{21}O_7I$ (584.35): C, 55.49; H, 3.62. Found: C, 55.45; H, 3.64.

N^4-Acetyl-1-(1,3,4-tri-*O*-benzoyl-6-deoxy-6-iodo-β-D-psicofuranosyl)cytosine (15b). A solution of N^4-acetylbis(trimethylsilyl)cytosine (3.5 g, 11.8 mmol)[38] and **9** (from 10 mmol of **8b**) was heated in benzene at 60 °C for 19 h in the presence of finely powdered mercuric cyanide (5.1 g, 20 mmol) and then evaporated. A filtered solution of the residue in chloroform was washed with aqueous sodium bicarbonate, 30% aqueous potassium iodide, and water. The dried solution was evaporated and the residue was chromatographed on a column of silicic acid (350 g) using benzene–ethyl acetate (3:2) giving 1.50 g (20%) of **15b** as a homogeneous foam: λ_{max} (MeOH) 231 nm (ϵ 46 000), 283 (8000), 298 (7700).

Anal. Calcd for $C_{33}H_{28}N_3O_9I$ (737.48): C, 53.74; H, 3.83; N, 5.70. Found: C, 54.20; H, 4.27; N, 5.55.

1-(6-Deoxy-β-D-*erythro*-hex-5-enofuran-2-ulosyl)cytosine (16). A. A solution of **15a** (695 mg, 1 mmol) in 0.06 M methanolic sodium methoxide (53 ml) was heated under reflux for 2 h and then cooled, neutralized with acetic acid, and evaporated. The residue was partitioned between water and chloroform and the aqueous phase was evaporated and coevaporated in the presence of silicic acid (1 g). The dried silicic acid was added to the top of a column containing 60 g of silicic acid. Elution of the column with chloroform–methanol (4:1) gave 230 mg (84%) of homogeneous, crystalline **16** which upon recrystallization from methanol gave 176 mg (61%) of pure product as the hemimethanolate with mp 185–186 °C: λ_{max} (0.1 N NaOH) 229 nm (ϵ 8600), 272 (8700); ORD (H_2O) $[\Phi]^{tr}_{286}$ 11 000°, $[\Phi]_{268}$ 0°, $[\Phi]^{tr}_{250}$ −9400°.

Anal. Calcd for $C_{10}H_{13}N_3O_5 \cdot \frac{1}{2}MeOH$ (271.24): C, 46.49; H, 5.57; N, 15.49. Found: C, 46.41; H, 5.74; N, 15.39.

B. A solution of **15a** (695 mg, 1 mmol) and DBN (0.25 ml, 2 mmol) in dimethylformamide (5 ml) was kept at room temperature for 24 h and then evaporated. The residue was treated with methanol (5 ml) and concentrated ammonium hydroxide (5 ml) for 64 h at room temperature and then evaporated leaving a residue that was dissolved in water (15 ml) and washed three times with ethyl acetate. The aqueous phase was evaporated and chromatographed on silicic acid as in A and crystallized from methanol giving 150 mg (55%) of **16** identical with that from A.

C. A solution of **15b** (1.25 g, 1.7 mmol) and DBN (0.5 g, 4 mmol) in dimethylformamide (10 ml) was kept at room temperature for 1.5 h and then worked up as in B. Crystallization from methanol gave 190 mg (44%) of pure **16** identical with that above. In one experiment a monomethanolate with mp 144–146 °C was obtained.

1-(1,3,4-Tri-*O*-benzoyl-6-deoxy-6-iodo-β-D-psicofuranosyl)-3-methoxycarbonyl-1,2,4-triazole (18a) and Its 5-Methoxycarbonyl Isomer 19. A solution of *N*-trimethylsilyl-3-methoxycarbonyl-1,2,4-triazole (5.42 g, 27.2 mmol)[45] and **9** (from 24.7 mmol of **8b**) in benzene (500 ml) was stirred at 60 °C for 2.5 h in the presence of finely divided mercuric cyanide (12.5 g, 49.4 mmol) and then evaporated. A filtered solution of the residue in chloroform was washed with aqueous sodium bicarbonate, 30% aqueous potassium iodide, and water, dried, and evaporated. The residue (19.6 g) was chromatographed on a column of silicic acid (1.4 kg) using benzene–ethyl acetate (92:8). Evaporation of the major peak followed by treatment with charcoal gave 8.64 g (49%) of **18a** as a homogeneous white foam: λ_{max} (dioxane) 231 nm (ϵ 4300), 270 (3000), 275 (3200), 283 (2600); $[\alpha]^{23}D$ −69.1° (c 1.0, dioxane).

Anal. Calcd for $C_{31}H_{26}N_3O_9I$ (711.4): C, 52.23; H, 3.68; N, 5.91. Found: C, 52.49; H, 3.72; N, 5.56.

Evaporation of a significant peak that was eluted from the column before **18a** gave 3.38 g (19%) of the 5-methoxycarbonyl derivative **19** as a foam: λ_{max} (dioxane) 231 nm (ϵ 42 200), 275 (3200), 282 (2700); $[\alpha]^{23}D$ −27.1° (c 1.0, dioxane).

Anal. Calcd for $C_{31}H_{26}N_3O_9I$ (711.4): C, 52.23; H, 3.68; N, 5.91. Found: C, 52.14; H, 3.95; N, 6.05.

In a separate experiment similar to that described above and giving **19** in 51% yield, the 6-chloro derivative (**18b**) was also isolated as a slightly more polar foam in 11% yield: λ_{max} (dioxane) 229 nm (ϵ 43 300), 275 (3300), 282 (2700); $[\alpha]^{23}D$ −80.1° (c 1.0, dioxane); mass spectrum (70 eV) *m/e* 585 (MH − Cl), 584 (M − Cl), 493, 495 (M − base), 484, 486 (M − CH_2OBz), 457 (*m/e* 493, 495 − HCl), 371, 373 (*m/e* 495, 495 − C_6H_5COOH), 362, 364 (*m/e* 484, 486 − C_6H_5COOH), 335 (*m/e* 371, 373 − HCl).

Anal. Calcd for $C_{31}H_{26}N_3O_9Cl$ (620.00): H, 4.23; N, 6.78. Found: H, 4.34, N, 6.67.

1-(1,3,4-Tri-*O*-benzoyl-6-deoxy-β-D-*erythro*-hex-5-enofuran-2-ulosyl)-3-methoxycarbonyl-1,2,4-triazole (20). A solution of **18a** (2.9 g, 4.08 mmol) and DBN (1.0 ml, 8 mmol) in dimethylformamide (60 ml) was kept at room temperature for 30 min and then evaporated. A solution of the residue in chloroform was washed with aqueous sodium thiosulfate and water, dried, and evaporated. Crystallization of the residue from ethanol gave 1.38 g (58%) of **20** with mp 153–154 °C: λ_{max} (dioxane) 230 nm (ϵ 37 100), 268 (2400), 275 (2900), 283 (2300).

Anal. Calcd for $C_{31}H_{25}N_3O_9$ (583.53): C, 63.80; H, 4.32; N, 7.20. Found: C, 64.06; H, 4.26; N, 7.18.

1-(6-Deoxy-β-D-*erythro*-hex-5-enofuran-2-ulosyl)-1,2,4-triazole-3-carboxamide (21). A solution of **20** (1.38 g, 2.37 mmol) in a mixture of methanol (20 ml) and concentrated ammonium hydroxide (20 ml) was kept at room temperature for 21 h and then evaporated. The residue was dissolved in water, washed five times with ether, and evaporated to dryness. A solution of the residue in methanol was decolorized with charcoal, evaporated in the presence of silicic acid (3 g), and added to a column of silicic acid (50 g). Elution with chloroform–methanol (4:1) followed by decolorization with charcoal gave 513 mg (85%) of **21** as a homogeneous white foam: λ_{max} (MeOH) 207 nm (ϵ 12 000); ORD (H_2O), plain positive $[\Phi]_{230}$ 6500°.

Anal. Calcd for $C_9H_{12}N_4O_5$ (256.22): C, 42.19; H, 4.72; N, 21.87. Found: C, 42.25; H, 4.88; N, 21.64.

1-(6-*O*-Acetyl-1,3,4-tri-*O*-benzoyl-β-D-psicofuranosyl)-3-methoxycarbonyl-1,2,4-triazole (18c). A solution of **18a** (2.25 g, 3.16 mmol) in acetic acid (80 ml) and water (0.8 ml) was stirred at 100 °C for 4.5 h in the presence of silver acetate (1.06 g, 6.34 mmol) and then evaporated. A solution of the residue in chloroform was washed with aqueous sodium bicarbonate and water, dried, and evaporated. The residue was chromatographed on a column of silicic acid (100 g) using benzene–ethyl acetate (4:1) giving 94 mg (5%) of crystalline **20** followed by 1.22 g (60%) of **18c** as a white foam: λ_{max} (dioxane) 212 nm (sh, ϵ 21 900), 230 (4600), 270 (sh, 3300), 275 (3100), 283 (2500).

Anal. Calcd for $C_{33}H_{29}N_3O_{11}$ (643.58): C, 61.58; H, 4.54; N, 6.53. Found: C, 61.72; H, 4.58; N, 6.23.

1-(β-D-Psicofuranosyl)-1,2,4-triazole-3-carboxamide (22). A solution of **18c** (1.3 g, 2 mmol) in methanol (15 ml) and concentrated ammonium hydroxide (15 ml) was kept at room temperature for 16 h and then evaporated. The residue was dissolved in water, washed with ether, and evaporated, leaving a residue that was chromatographed on silicic acid (50 g) using chloroform–methanol (3:1). The major peak was decolorized with charcoal and evaporated leaving 387 mg (71%) of **22** as a homogeneous foam that crystallized very slowly from ethanol at −18 °C with mp 66–68 °C dec, λ_{max} (0.1 N HCl) 208 nm (ϵ 1800).

Anal. Calcd for $C_9H_{14}N_4O_6$ (274.23): C, 39.42; H, 5.15; N, 20.43. Found: C, 39.39; H, 5.28; N, 20.28.

6-*O*-Benzoyl-1,2:3,4-di-*O*-isopropylidene-β-D-psicofuranose (23). A solution of **7c** (3.7 g, 10 mmol) and lithium benzoate (2.5 g, 20 mmol) in dimethylformamide (100 ml) was kept at 100 °C for 16 h and then evaporated. The residue was partitioned between ether (100 ml) and water (3 × 50 ml) and the ether layer was dried and evaporated. Crystallization of the residue from aqueous methanol gave 3.28 g (90%) of **23** with mp 72–72.5 °C.

Anal. Calcd for $C_{19}H_{24}O_7$ (364.38): C, 62.62; H, 6.64. Found: C, 62.70; H, 6.74.

6-*O*-Benzoyl-D-psicofuranose (24a). A mixture of **23** (29.5 g, 81 mmol) and Bio-Rad AG 50W (H^+) resin (60 ml) in water (300 ml) was stirred at 65 °C for 12 h, then stored at 5 °C for 18 h and filtered. The filtrates were adjusted to pH 6 with barium carbonate and filtered and the solids were washed with acetone. Evaporation of the filtrates left a residue that was coevaporated with toluene–ethanol (1:1) and dried under high vacuum giving 22.4 g (97%) of **24a** as a foam that was

sufficiently pure for direct use in the next step. An analytical sample was prepared by preparative TLC using chloroform–methanol (4:1), elution of the ultraviolet-absorbing band giving the mixed anomers of **24a** as a white foam.

Anal. Calcd for $C_{13}H_{16}O_7$ (284.26): C, 54.93; H, 5.67. Found: C, 54.88; H, 5.97.

1,2,3,4,6-Penta-*O*-benzoyl-D-psicofuranose (24b). Benzoyl chloride (100 ml, 0.86 mol) was added dropwise over 50 min to a stirred solution of **24a** (22.8 g, 80 mmol) in pyridine (500 ml) at 0 °C. After a further 24 h at room temperature, methanol (50 ml) was added and the mixture was evaporated to dryness. A solution of the residue in chloroform was washed with water, dried, and evaporated, leaving a residue that was largely freed from methyl benzoate by drying at 50 °C under high vacuum for 8 h. The product (69 g) was then purified by chromatography on a column of silicic acid (2.9 kg) using elution with benzene–ethyl acetate (98:2) until **24b** appeared followed by a gradient of ethyl acetate (2–7.5%) in benzene. Evaporation of the major peak left 32.59 g (53%) of pure **24b** as a foam. An analytical sample was prepared by preparative TLC using benzene–ethyl acetate (19:1).

Anal. Calcd for $C_{41}H_{32}O_{11}$ (700.67): C, 70.28; H, 4.60. Found: C, 70.05; H, 4.43.

1-(1,3,4,6-Tetra-*O*-benzoyl-β-D-psicofuranosyl)cytosine (25a). **A.** Anhydrous hydrogen bromide was passed through a solution of **24b** (3.5 g, 5 mmol) in dichloromethane (40 ml) at 0 °C for 15 min and the solution was then kept at 0 °C for 1.25 h and evaporated to dryness. The residue was coevaporated four times with a 3:1 mixture of toluene and dichloromethane (30 ml) leaving semicrystalline, crude **24c.** This material and bis(trimethylsilyl)cytosine (1.5 g, 6 mmol) were dissolved in benzene and stirred at 60 °C for 1.5 h in the presence of finely powdered mercuric cyanide (3.75 g, 15 mmol). The mixture was then evaporated and a solution of the residue in chloroform was filtered through Celite. The filtrate was washed with aqueous sodium bicarbonate, 30% aqueous potassium iodide, and water, dried, and evaporated. The residue was chromatographed on a column of silicic acid (250 g) using chloroform–acetone (3:2) and giving 1.13 g (33%) of **25a** as a TLC homogeneous foam. An analytical sample was prepared by preparative TLC using chloroform–methanol (98:2): λ_{max} (MeOH, H^+) 230 nm (ε 5700), 281 (15 300).

Anal. Calcd for $C_{38}H_{31}N_3O_{10}$ (689.65): C, 66.18; H, 4.53; N, 6.09. Found: C, 65.80; H, 4.81; N, 6.47.

B. To a solution of **24c** (obtained from 5 mmol of **24b** as described above) in acetonitrile (100 ml) were added cytosine (670 mg, 6 mmol), mercuric cyanide (3.75 g, 15 mmol), and stannic chloride (1.2 ml, 10 mmol). The reaction mixture was stirred at 60 °C for 1.5 h and the brown solution was then evaporated. The residue was dissolved in chloroform and filtered. A saturated solution of sodium bicarbonate was used to neutralize the filtrate and a light precipitate was removed by filtration. The organic layer was washed with 30% potassium iodide and water, dried, and evaporated. The residue (3 g) was purified by chromatography as described above and gave 1.33 g (33%) of **25a** as a TLC homogeneous foam identical with that above.

1-(β-D-Psicofuranosyl)cytosine (25b). A suspension of **25a** (1.0 g, 1.45 mmol) in a mixture of methanol (10 ml) and concentrated ammonium hydroxide (15 ml) was stirred at room temperature for 24 h and the mixture (from which crystalline **25b** had separated) was evaporated, leaving a crystalline residue that was thoroughly washed with ethyl acetate. Recrystallization from water gave 321 mg (72%) of **25b** as the dihydrate which lost water at 95–110 °C and melted at 208–209 °C dec, unchanged upon recrystallization (reported[9c] mp 207–208 °C): λ_{max} (0.1 N HCl) 214 nm (ε 9700), 281 (1000); λ_{max} (0.1 N NaOH) 226 nm (ε 9100), 273 (9400); $[\alpha]^{23}D$ −33.8° (c 1.0, Me_2SO)

Anal. Calcd for $C_{10}H_{15}N_3O_6 \cdot 2H_2O$ (309.27): C, 38.83; H, 6.19; N, 13.59. Found: C, 38.96; H, 6.15; N, 13.51.

Registry No.—**1**, 2004-04-8; **2a**, 58463-03-9; **2b**, 58463-04-0; **2c**, 58463-05-1; **3**, 20535-04-0; **4**, 25018-67-1; **5**, 18422-53-2; **6**, 18422-54-3; **7a**, 34626-95-4; **7b**, 58501-81-8; **7c**, 38084-06-9; **8a**, 58463-06-2; **8b**, 58463-07-3; **8c**, 58463-08-4; **9**, 58463-09-5; **10**, 3621-71-4; **11a**, 58463-10-8; **11b**, 58463-11-9; **11c** 58463-12-0; **12a**, 58463-13-1; **12c**, 58463-14-2; **13**, 58463-15-3; **14**, 58463-16-4; **15a**, 58463-17-5; **15b**, 58463-18-6; **16**, 58463-19-7; **17**, 58463-20-0; **18a**, 58463-21-1; **18b**, 58463-22-2; **18c**, 58463-23-3; **19**, 58463-24-4; **20**, 58463-25-5; **21**, 58463-26-6; **22**, 58463-27-7; **23**, 58501-82-9; **24a**, 58463-28-8; **24b**, 58463-29-9; **24c**, 54401-10-4; **25a**, 58463-30-2; **25b**, 53318-75-5; 5′-*O*-trityladenosine methyltriphenoxyphosphonium iodide methyl, 17579-99-6; methyltriphenoxyphosphonium iodide, 4167-91-3; fructose, 57-58-7; acetone, 67-64-1; *p*-toluenesulfonyl chloride, 98-59-9; sodium iodide, 7681-82-5; *p*-nitrobenzoyl chloride 122-04-3; N^6-hexanoyladenine, 21043-28-7; N^6-benzoylchloromercuriadenine, 17187-65-4; bis(trimethylsilyl)cytosine, 18037-10-0; N^4-acetylbis(trimethylsilyl)cytosine, 18027-23-1; *N*-trimethylsilyl-3-methoxycarbonyl-1,2,4-triazole, 40372-08-5.

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A New Alkylation Reagent for Seleno- and Thio-Substituted Nucleosides and Related Compounds

Chyng-Yann Shiue and Shih-Hsi Chu*

Division of Biological and Medical Sciences, Brown University, Providence, Rhode Island 02912

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The mixture of dialkyl disulfide (or diselenide) and tri-*n*-butylphosphine was found to be a new alkylation reagent for seleno- and thio-substituted nucleosides and related compounds.

5′-Deoxy-5′-(methylthio)adenosine is known to inhibit the transmethylation reactions of *S*-adenosyl-L-methionine in vitro.[1,2] Its analogues were usually prepared by multistep syntheses.[3-5] Recently, a convenient method was reported for the synthesis of 5′-*S*-alkylthio-5′-deoxyribonucleosides and nucleotides.[6,7] For example, after treatment of adenosine with dimethyl disulfide and tri-*n*-butylphosphine in DMF for 24 h, 5′-*S*-methylthio-5′-deoxyadenosine was isolated in 73% yield.[7] However, in application of this reaction to synthesize some 5′-*S*-alkylthio-5′-deoxy-6-thio (or seleno) ribonucleosides from the corresponding 6-thio (or seleno) ribonucleosides, we have found that the reaction took an unexpected course.

After treatment of 6-seleno-9-(β-D-ribofuranosyl)purine[8,9] with excess of dimethyl disulfide and tri-*n*-butylphosphine in DMF at room temperature for 2 h, instead of the expected 5′-*S*-methylthio-5′-deoxy-6-selenoinosine, 6-methylseleno-9-(β-D-ribofuranosyl)purine (I)[10] was isolated in 63% yield. Other examples of this reaction are indicated in Scheme I and Table I. Structures of these compounds were verified by elemental analysis, uv, and NMR data and compared with authentic samples.

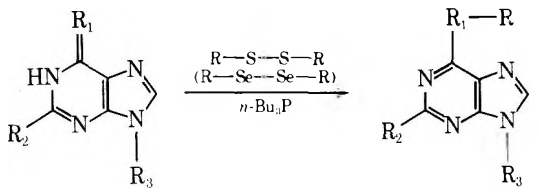
In order to explore the limitation of this new methylation reagent, 6-selenopurine was treated with a variety of disulfides (or diselenides) and tri-*n*-butylphosphine. After treatment of 6-selenopurine with dibenzyl disulfide and tri-*n*-butylphosphine in DMF for 2 h, ultraviolet spectral monitoring indicated that 6-selenopurine [λ_{max} (MeOH) 362 nm] was completely converted to 6-benzylselenopurine [λ_{max} (MeOH) 302 nm]. However, after the mixture was distilled in vacuo at 125 °C and the residue washed with petroleum ether and then recrystallized from H_2O, the product isolated was 6-benzylthiopurine [λ_{max} (MeOH) 292 nm]. This unexpected side re-

Table I. Alkylthio- and Alkylselenopurines Prepared by the Reaction of Thio- and Selenopurines with a *n*-Butylphosphine and Dialkyl Disulfide[a]

Thio- (or seleno-) purines	Dialkyl disulfide	Product	Reaction time	Yield %	NMR, δ
6-Seleno-9-(β-D-ribofuranosyl)purine[8,9]	Me–S–S–Me	I[10]	2 h	63	8.77 (1 H) 8.73 (1 H) 6.07 (1 H) 2.60 (3 H)
6-Selenopurine[12]	Me–S–S–Me	II[12]	Overnight	50	8.77 (1 H) 8.54 (1 H) 2.63 (3 H)
6-Mercaptopurine[13]	Me–S–S–Me	III[20]	Overnight	54	8.70 (1 H) 8.43 (1 H) 2.70 (3 H)
6-Mercaptopurine riboside[14]	Me–S–S–Me	IV[21,22]	4 h	12	8.77 (1 H) 8.71 (1 H) 6.07 (1 H) 2.71 (3 H)
6-Selenoguanosine[10,15,16]	Me–S–S–Me	V[10]	3 h	32	8.21 (1 H) 6.53 (2 H) 5.85 (1 H) 2.50 (3 H)
8-Selenoguanosine[17]	Me–S–S–Me	VI[17]	1 h	33	6.35 (2 H) 5.68 (1 H) 2.48 (3 H)
4-Thiouracil[18,19]	Me–S–S–Me	VII[23]	Overnight	35	7.43 (1 H) 6.18 (1 H) 2.48 (3 H)
6-Seleno-9-(β-D-ribofuranosyl)purine 3′,5′-cyclic phosphate[9,16]	Me–S–S–Me	VIII[9]	2 h	75	8.73 (1 H)[9] 8.51 (1 H) 2.19 (3 H) 8.70 (1 H) 8.40 (1 H)
6-Mercaptopurine[13]	Bzl–S–S–Bzl	IX[24]	2 days	50	7.27 (5 H) 4.67 (2 H) 8.70 (1 H) 8.40 (1 H)
6-Selenopurine[12]	Bzl–Se–Se–Bzl	X	2 days	45	7.27 (5 H) 4.70 (2 H)

[a] Satisfactory analytical data (±0.4% for C, H, N) for all new compounds (I, II, III, VI, IX, X) were submitted for review.

Scheme I

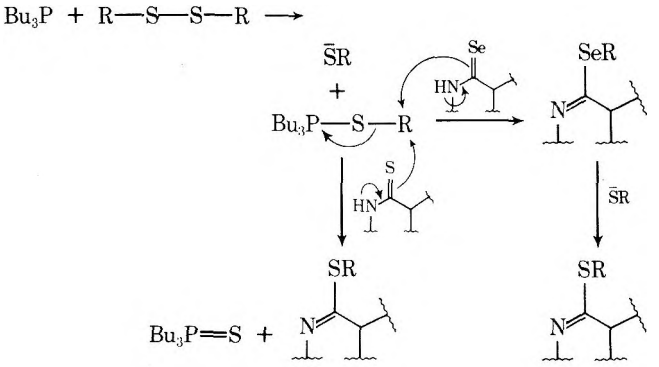


I-X

I	$R = CH_3$,	R_1 = Se,	R_2 = H,	R_3 = β-D-ribofuranosyl
II	$R = CH_3$,	R_1 = Se,	R_2 = H,	R_3 = H
III	$R = CH_3$,	R_1 = S,	R_2 = H,	R_3 = H
IV	$R = CH_3$,	R_1 = S,	R_2 = H,	R_3 = β-D-ribofuranosyl
V	$R = CH_3$,	R_1 = Se,	$R_2 = NH_2$,	R_3 = β-D-ribofuranosyl
VI	8-seleno-guanosine			8-methylseleno-guanosine
VII	4-thiouracil			4-methyl-thiouracil
VIII	$R = CH_3$,	R_1 = Se,	R_2 = H,	R_3 = 3′,5′-cyclic phosphoribosyl
IX	$R = C_6H_5CH_2$,	R_1 = S,	R_2 = H,	R_3 = H
X	$R = C_6H_5CH_2$,	R_1 = Se,	R_2 = H,	R_3 = H

action is presumably due to the fact that the benzylseleno group was displaced by the benzylthio group at elevated temperatures. Indeed, when 6-benzylselenopurine was treated with dibenzyl disulfide and tri-*n*-butylphosphine in DMF and the reaction mixture was distilled at 125–130 °C, 6-benzylthiopurine was isolated. 6-Benzylselenopurine also reacted with benzyl mercaptide anion in refluxing DMF to give 6-benzylthiopurine. Treatment of 6-mercaptopurine with dibenzyl disulfide and tri-*n*-butylphosphine gave 6-benzylthiopurine as expected. Likewise, 6-selenopurine reacted with dibenzyl diselenide and tri-*n*-butylphosphine to give 6-benzylselenopurine.

The mechanism of this alkylation reaction is probably similar to those proposed by Kharasch et al.[11] for the dealkylation of dialkyl disulfide by mercaptide anion and can be shown as follows:



These results demonstrate that the mixture of dialkyl disulfide (or deselenide) and tri-*n*-butylphosphine was a new alkylation reagent for seleno- and thio-substituted nucleosides and related compounds.

Experimental Section

Ultraviolet spectra were determined on a Perkin-Elmer Model 402 spectrophotometer. NMR spectra were measured on a Varian A-60A spectrometer in Me_2SO-d_6 with Me_4Si as the internal standard. Elemental analyses were performed by Midwest Microlab, Indianapolis, Ind.

In a typical experiment, a solution of 400 mg (1.15 mmol) of 6-seleno-9-(β-D-ribofuranosyl)purine,[8,9] 1 g (10 mmol) of dimethyl disulfide, and 2 g (10 mmol) of tri-*n*-butylphosphine in 5 ml of DMF was stirred at room temperature for 2 h. The solution was evaporated and the oily residue was distilled at reduced pressure. Ether was added into the residue and the precipitates were filtered by suction and dried to give 250 mg (63%) of I.[10] The analytical sample was recrystallized from H_2O.

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Registry No.—I, 30902-29-5; II, 58540-76-4; III, 50-66-8; IV, 342-69-8; V, 30902-27-3; VI, 55921-92-1; VII, 35551-31-6; VIII, 56477-18-0; IX, 724-34-5; X, 58540-77-5; 6-seleno-9-(β-D-ribofuranosyl)purine, 40093-99-0; 6-selenopurine, 5270-30-4; 6-mercaptopurine, 50-44-2; 6-mercaptopurine riboside, 653-58-7; 6-selenoguanosine, 29411-74-3; 8-selenoguanosine, 55921-90-9; 4-thiouracil, 591-28-6; 6-seleno-9-(β-D-ribofuranosyl)purine 3′,5′-cyclic phosphate, 56477-08-8; Me-S-S-Me, 624-92-0; Bzl-S-S-Bzl, 150-60-7; Bzl-Se-Se-Bzl, 1482-82-2; tri-*n*-butylphosphine, 998-40-3.

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Studies of Mixed-Valence Diferrocenyl Selenide and Diferrocenyl Diselenide

P. Shu, K. Bechgaard, and D. O. Cowan*

Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218

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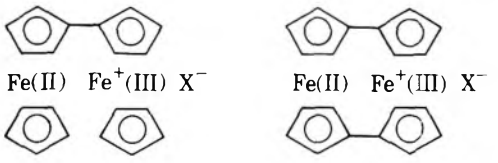
New synthetic routes were devised for the preparation of diferrocenyl selenide (I) and diferrocenyl diselenide (II). The electrochemical and spectroscopic properties of these compounds and their corresponding mono- and dications are reported. The relatively large separation between the first and second oxidation potential of I and II (0.22, 0.14 V) compared with the corresponding methylene and ethylene bridged ferrocenes (0.17, 0.00 V) indicates that the selenium group, because of its polarizability, can effectively transmit the inductive effect of the ferrocenyl substituent. Inasmuch as no intervalence transfer transition (near infrared) was observed for either the monocation of I or of II, these compounds are type I mixed-valence salts. This suggests that electron transfer, both thermal and optical, requires some delocalization via the bridging group. The relatively long C–Se bond and the resulting small resonance integral mitigate against any effective electron transfer in these cations.

Mixed valence compounds, which are composed of two identical or similar moieties in different oxidation states, play an important role in biological, organic, and inorganic reactions. These compounds also exhibit interesting magnetic, electronic, and optical properties which differ from those of similar species not containing paired moieties. Fe_3O_4, a mixed valence compound of FeO and Fe_2O_3, has an electrical conductance 10^6 times greater than that of Fe_2O_3. These phenomena have been explained as the result of delocalization between the sites in the mixed valence species. A mixing parameter α is defined and used to express the extent of this delocalization.[2] The ground state of the mixed valence compound can be expressed in terms of ϕ_i, ϕ_j which are the wave functions of donor and acceptor moieties, and α. When $\alpha = 0$, there is no interaction between components.

$$\psi_G = \sqrt{1-\alpha^2}\,\phi_i + \alpha\phi_j$$

A totally delocalized mixed valence compound, obtained when $\alpha = 0.707$, should possess a new set of properties. Intermediate cases may possess new properties besides the ones inherited from other progenitors. For example, an "intervalence transfer" band[2a,3] in the near infrared at 1500–1900 nm has been found in monocations of biferrocenes in



addition to ferrocene and ferrocenium absorptions in the uv and visible regions. A transition involving an electron transfer between two metallike e_{2g} orbitals has been proposed to account for this transition.

$$[^1A_{1g}(e_{2g})^4(a_{1g})^2]_i \sim [^2E_{2g}(e_{2g})^3(a_{1g})^2]_j \xrightarrow{h\nu}$$

$$[^2E_{2g}(e_{2g})^3(a_{1g})^2]_i \sim [A_{1g}(e_{2g})^4(a_{1g})^2]_j \quad (1)$$

The mechanism of the intervalence transition still remains uncertain. The study of metallocenes, especially biferrocenes, should enable one to learn more about this phenomenon, because small ligand and functional group changes can be designed and incorporated into such molecules conveniently and the resulting differences may be studied. The intervalence transfer may be accomplished in two different ways, through ligand and through space. The first takes place through a bridge or a "single" bond, between the ligands of two ferrocene units. The second occurs via direct metal–metal interaction. It is often difficult to determine which mechanism is dominant in a particular case. By the proper choice of model systems, one should be able to distinguish qualitatively as to which is the more important mechanism for electron transfer in the ferrocene–ferrocenium system.

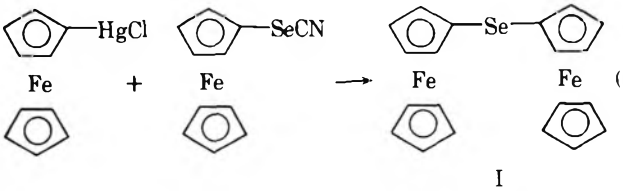
We have observed a near infrared transition for several mixed-valence bridged ferrocene molecules where the bridging group is in (C-π) conjugation with the cyclopentadienyl rings (for example, the monocation of diferrocenylacetylene[7]).

However, to date there has been little work reported regarding the effect of other bridging groups on electron transfer between ferrocene moieties and on the near infrared transition. Selenium could serve as a transmitting bridge in biferrocenes. The relatively long Se–Se (2.29 Å)[4] and C–Se (1.93 Å) bonds might minimize the through space and even through ligand interaction in these selenium bridged biferrocenes.

It is the purpose of this paper to report the synthesis of diferrocenyl selenide (I), diferrocenyl diselenide (II), and their mono- and dications, and to examine the interaction between the two ferrocene moieties of the monocations of I and II.

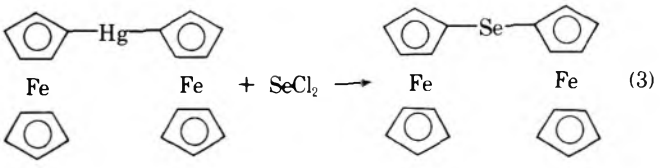
Results and Discussion

Synthesis. We find that diferrocenyl selenide (I) can be prepared by direct coupling of chloromercuriferrocene and ferrocenyl selenocyanate in quantitative yields (eq 2). Compound I was first synthesized by Nesmeyanov and coworkers[8] via the reaction of diferrocenylmercury and selenium dichloride in 21% yield (eq 3). Diferrocenyl diselenide



I

100%



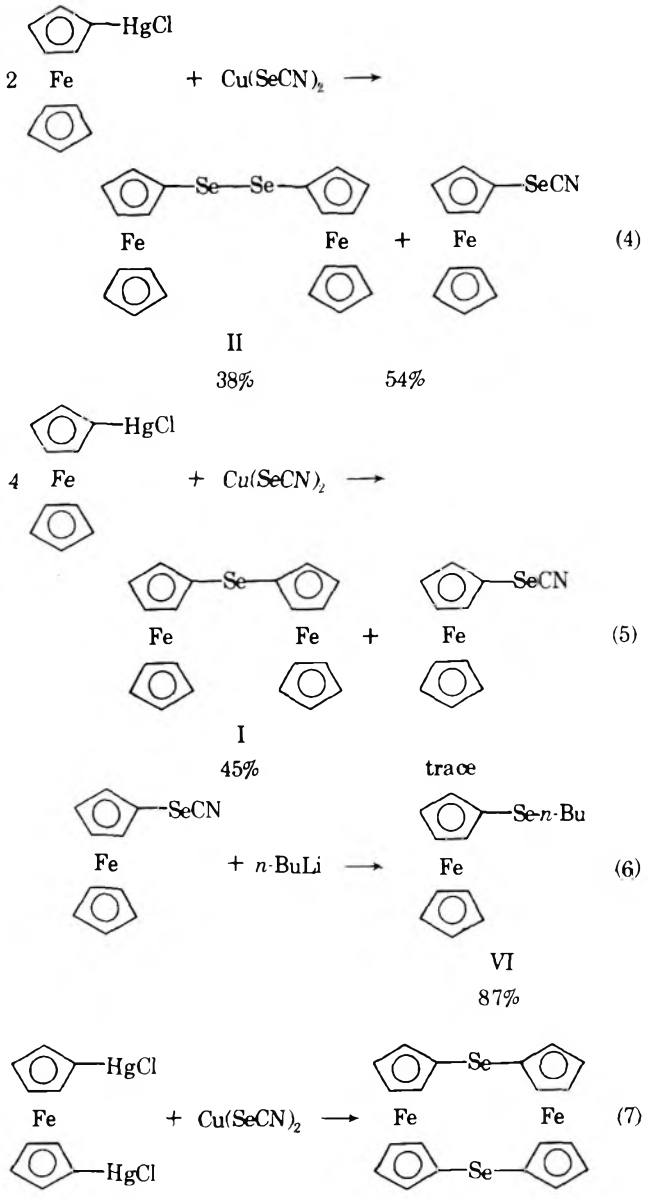
I

21%

Table I. Half Wave Potentials[a] of Bridged Biferrocenes

Compd	Solvent	$E_{1/2}$ (1)	$E_{1/2}$ (2)	$\Delta E_{1/2}$	Ref
Diferrocenyl selenide (I)	CH_3CN	0.46	0.68	0.22	This work
Diferrocenyl diselenide (II)	CH_3CN	0.53	0.67	0.14	This work
Diferrocenemethane (III)	CH_3CN (90% EtOH)	0.39 (0.30)	0.56 (0.40)	0.17 (0.10)	6, 9
Diferrocenylethane (IV)	CH_3CN	0.37	0.37	0	9
[1.1]Ferrocenophane (V)	90% EtOH	0.25	0.44	0.19	6
Diferrocenylacetylene (VI)	CH_2Cl_2[b]	0.61	0.745	0.135	7
Ferrocenyl *n*-butylselenide (VI)	CH_2CN	0.405			This work
Methylferrocene (VIII)	CH_3CN	0.305			[c]

[a] Volts vs. SCE. [b] n-Bu_4NBF_4 (0.2 M), otherwise Et_4NClO_4 (0.1 M) for those which are unnoted. [c] Unpublished results: D. O. Cowan and C. LeVanda.



(II) was obtained as a coproduct with ferrocenyl selenocyanate in the reaction of copper(II) selenocyanate and chloromercuriferrocene in moderate yields (38%) (eq 4). When this reaction was carried out under an inert gas (N_2, Ar) and under anhydrous conditions, a mixture of ferrocenyl selenide (I) and ferrocenyl selenocyanate was obtained (eq 5). *Ferrocenyl n-butylselenide* (VI), a *reference compound*, was prepared by the reaction of *n*-butyllithium and ferrocenyl selenocyanate (eq 6). Attempts to prepare bis(dicyclopentadienyl selenide)diiron via the reaction shown in eq 7 were not successful.

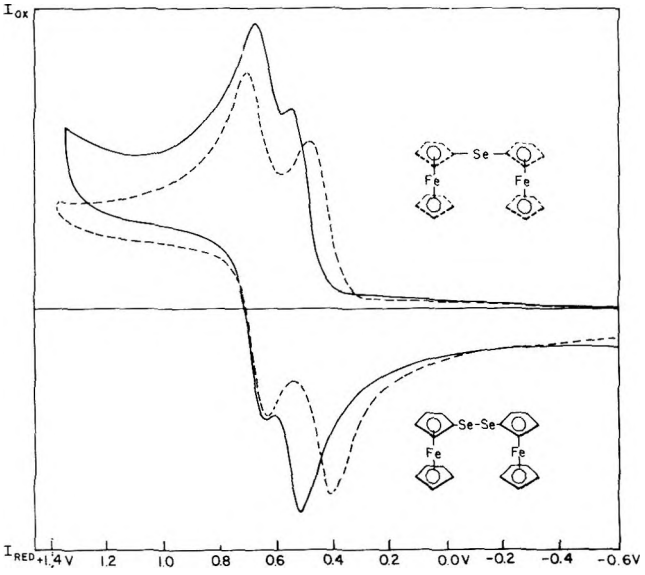


Figure 1.

Electrochemistry. The cyclovoltammograms of I and II are illustrated in Figure 1 and the results are summarized in Table I. As demonstrated by the cyclovoltammogram, both I and II undergo two reversible one-electron oxidations to their mono- and dications, respectively (eq 8).

$$\mathrm{I} \overset{-e}{\rightleftarrows} \mathrm{I}^{+} \overset{-e}{\rightleftarrows} \mathrm{I}^{2+}$$

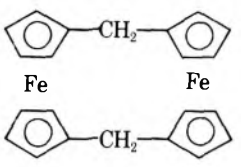
$$\mathrm{II} \overset{-e}{\rightleftarrows} \mathrm{II}^{+} \overset{-e}{\rightleftarrows} \mathrm{II}^{2+} \qquad (8)$$

Peak separations were found to be close to 60 mV at 25 °C and peak ratios were found to be unity.

Acetonitrile solutions of I^+ and II^+ were prepared by coulometric oxidation of *I* and *II* with *1.0 F/mol* of current. The stability and identity of those monocations were confirmed by cyclic voltammetry and polarography. Exhaustive oxidation in acetonitrile of I and II leads to decomposition. The failure to obtain stable I^{2+} and II^{2+} in acetonitrile solutions is probably due to a trace of moisture which is difficult to remove. However, "stable" solutions of I^{2+} and II^{2+} could be obtained by oxidation of I and II with precisely 2 F/mol in CH_2Cl_2. Identity and stability of those dications were again demonstrated by cyclic voltammetry and polarography. The electrochemically generated solutions of the mono- and dications of I and II are stable enough to permit the recording of their absorption spectra under inert conditions.

It has been proposed by Watts et al.[6] that in bridged biferrocenes, their ΔE values (the differences between the first and second half wave potentials of biferrocenes) is an indication of the amount of electronic interaction between

the two portions of the molecule. However, according to the recent report of Cowan and co-workers,[7] diferrocenylacetylene monocation has a near infrared transition even though it has a rather small ΔE value (0.13 V). However, the differences between two oxidation potentials of a bridged diferrocene measured under similar conditions do give a reasonable measurement of the interaction between two ferrocene moieties in a given series of compounds. For example, the ΔE value of diferrocenemethane (III) in 90% EtOH is 0.1 V which increases to 0.19 V in the case of [1.1]-ferrocenophane (V) (Table I) owing to the additional



[1.1]ferrocenophane (V)

bridge. When the bridge in diferrocenemethane is lengthened by one more CH_2 group, the ΔE for diferrocenylethane is reduced to zero.

Diferrocenemethane (III) has a ΔE value of 0.17 V in acetonitrile which is less than that of diferrocenyl selenide (I) (ΔE = 0.22 V), suggesting less intramolecular interaction in III. This interaction is further reduced to zero in diferroceneethane (IV) while its selenium analogue still has a ΔE value of 0.14 V. This finding suggests that the $-CH_2-$ group is a more insulating group than is selenium. Two methylene groups can essentially isolate the two ferrocene units in IV, eliminating both through space and through ligand interactions. It is known that the C–Se bond and and Se–Se bond are much longer than the C–C bond. it is reasonable, therefore, to believe that through space interaction is relatively unimportant in diferrocenyl diselenide (II) and diferrocenyl selenide (I). Consequently, the increased interaction between the ferrocene moieties in diferrocenyl selenide and diferrocenyl diselenide vs. diferrocenemethane and diferroceneethane is most likely a through ligand inductive (σ bond) effect which the more polarizable selenium transmits more efficiently.

Electronic Spectroscopy. The visible and near infrared spectra were measured for the monocations of I and II. No near infrared band was observed in either species. However, the ferrocenium absorption[10] of $^2E_{2g} \rightarrow {}^2E_{2u}$ at ~617 nm was shifted to 860 (ϵ 1350) and 840 nm (ϵ 550) for the monocations of I and II, respectively, which is not inconsistent with the conclusion that the selenium moiety transmits the inductive effect more effectively than the $-CH_2-$ group. Such a shift was also observed in the case of the [1.1]ferrocenophane monocation (750 nm, ϵ 3350),[11] and a similar absorption was found in the monocation of *n*-butylferrocenyl selenide at 910 nm, ϵ 375. This is consistent with the proposed origin of the red shifted ligand-to-metal transitions. The assignment of this ferrocenium transition of $^2E_{2g} \rightarrow {}^2E_{2u}$ is further strengthened by the fact that in the dications of I and II, absorptions at 810 (ϵ 1000) and 780 nm (ϵ 1000), for I^{2+} and II^{2+}, respectively, were observed.

Conclusion

From the absence of an intervalence transfer transition (near infrared transition) for the monocations of diferrocenyl selenide (I) and diferrocenyl diselenide (II), we conclude that these two compounds are class I materials where the –Se– group, like the $-CH_2-$ group, does not act as an effective bridge for electron transfer ($\alpha \approx 0$). However, based on the electrochemistry, we conclude that the –Se– bridge does allow a larger inductive communication between the two ferrocene moieties than does the $-CH_2-$ bridge. This conclusion is consistent with the red shift for the ligand-to-metal transition of the ferrocenium portion of the monocations. The lack of near infrared absorption for I^+ and II^+ plus the fact that diferrocenylacetylene has a small ΔE value yet possesses a near infrared transition strongly suggest that there is no correlation between intervalence transition and ΔE values.

Experimental Section

General. Melting points were measured on a Thomas-Hoover Uni-Melt apparatus or a Mel-Temp apparatus and are uncorrected. Microanalyses were performed by the Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were recorded with a Perkin-Elmer 457 spectrometer. Ultraviolet, visible, and near infrared spectra were taken with a Cary 14 spectrophotometer. ^1H NMR spectra were recorded on a JEOL MH 100 spectrometer. Mass spectra were taken on a Hitachi Perkin-Elmer RMU-6 mass spectrometer.

Cyclic voltammograms were obtained with a PAR-175 universal programmer and a PAR-173 potentiostat using a standard three-electrode configuration. The working electrode, a platinum button (Beckman), and the reference, a saturated calomel electrode, were connected via a salt bridge containing Et_4NClO_4 in CH_3CN. All electrochemical measurements were performed under argon. The current function $[i_p/V^{1/2}C]$ was constant over a wide range of sweep rate (25–300 mV/s), and a 1:1 relationship for the anodic and cathodic peak currents was observed. These data indicate the electrochemical reversibility of the couples.

In preparative experiments, 0.05 mmol of the ferrocene compound was oxidized (0.1 M in electrolyte) using a platinum basket electrode in a cell holding 50–100 ml of solvent. The cations were generated by constant current oxidation.

Samples for absorption spectra were transferred under argon from the electrolysis cell through 2-mm Teflon tubing to a 1-cm quartz flow cell which has been previously rinsed with the electrolysis solution and then sealed.

Diferrocenyl Selenide (I). Method A. Ferrocenyl selenocyanate (29 mg, 0.1 mmol) and chloromercuriferrocene (43 mg, 0.1 mmol) were refluxed in 15 ml of acetonitrile for 2 h. The reaction mixture showed no trace of starting materials on a TLC sheet (alumina, 1:1 benzene–heptane). This mixture was first filtered through neutral alumina. Upon drying and removal of the solvent, a residue was obtained. Alumina dry column separation with 1:1 CH_2Cl_2–heptane developer yielded I (45 mg, 100%). Recrystallization from heptane yielded crystalline I with mp 161–162 °C.

Method B. Chloromercuriferrocene (1.05 g, 2.5 mmol) was refluxed with freshly prepared $Cu(SeCN)_2$ (0.62 mmol) in 50 ml of dry acetonitrile under Ar for 2 h. The reaction mixture was first filtered through neutral alumina. After drying over anhydrous $MgSO_4$ and removal of the solvent, a yellow residue was obtained. Separation with an alumina dry packed column developed with CH_2Cl_2–heptane (1:1) yielded traces of ferrocenyl selenocyanate and diferrocenyl diselenide (II) along with the desired diferrocenyl selenide (I, 500 mg, 45% yield): mass spectrum (70 eV) *m/e* (rel intensity) 452 (20), 451 (27), 450 (92) (M^+ for $C_{20}H_{18}{}^{56}Fe_2{}^{80}Se$), 449 (15), 448 (57), 447 (20), 446 (24), 320 (25), 307 (20), 306 (100), 305 (18), 305 (18), 304 (80), 302 (10), 249 (20), 225 (10) (M^{2+} for $C_{20}H_{18}{}^{56}Fe^{80}Se$), 192 (18), 186 (28), 129 (18), 128 (15), 121 (24), 71 (20), 57 (34), 56 (21); NMR ($CDCl_3$, Me_4Si) δ 4.05 (4 H, m), 4.1 (10 H, s), 4.22 (4 H, m); ir (KBr) 3100 w, 1413 w, 1390 w, 1150 m, 1108 m, 1000 m, 880 s, 820 s, 490 cm^{-1} s; uv (CH_3CN) 224 nm (ϵ 18 000), 227 (18 500), 262 (10 000), 440 (400).

Ferrocenyl Selenocyanate and Diferrocenyl Diselenide (II). This preparation was in part derived from the procedure of Nefedov[12] in his synthesis of ferrocenyl selenocyanate. Chloromercuriferrocene (7 g, 16 mmol) was heated to reflux temperature with freshly prepared $Cu(SeCN)_2$ (8 mmol) in 250 ml of dried acetonitrile for 2 h. The reaction mixture was first filtered through neutral alumina. A yellow residue was obtained after removal of the solvent. This residue was placed on an alumina dry column and developed with 1:1 CH_2Cl_2 and heptane. Two fractions were obtained: diferrocenyl diselenide (II, 1.61 g, 38% yield), mp 181–183 °C, and ferrocenyl selenocyanate (1.51 g, 54% yield) with a lower R_f value (II): NMR ($CDCl_3$) δ 4.2 (10 H, s), 4.28 (4 H, half of an A_2B_2 pattern, J = 1.8 Hz), 4.33 (4 H, another half of an A_2B_2 pattern, J = 1.8 Hz); ir (KBr) 3080 w, 1400 w, 1380 w, 1145 m, 1100 m, 1040 w, 1010 m, 995 m, 875 m, 815 s, 500 cm^{-1} vs; mass spectrum (70 eV) *m/e* (rel intensity) 530 (15) (M^+ of $C_{20}H_{18}{}^{56}Fe^{80}Se^{80}Se$),

528 (15), 450 (24), 385 (10). 320 (22), 318 (15), 306 (29), 304 (31), 267 (21), 266 (35), 265 (100), 264 (22), 263 (60), 262 (24), 186 (56), 128 (62), 127 (36), 121 (45), 56 (55).

Anal. Calcd for $C_{20}H_{18}Fe_2Se_2$: C, 45.45; H, 3.41. Found: C, 45.55; H, 3.39.

***n*-Butylferrocenyl Selenide (VI).** Ferrocenyl selenocyanate (291 mg, 1 mmol) stirred with 0.5 ml of *n*-butyllithium (2.2 M) in 10 ml of dried *n*-heptane at room temperature in a Schlenck reaction tube under argon for 4 h. A clear yellow solution was obtained. A drop of water was added to decompose unreacted *n*-butyllithium. This solution was then extracted with ether and washed with water. After drying over anhydrous $MgSO_4$ and removal of the solvent, an orange-yellow oil was obtained. After alumina dry column purification (developed with 1:1 CH_2Cl_2 and *n*-heptane), crude VI was obtained (280 mg, 87%). An analytical sample was obtained by further purification with high pressure liquid chromatography (porasil C_{18} column, 15:85 ethylene chloride in *n*-heptane): mass spectrum (70 eV) *m/e* (rel intensity) 324 (14), 323 (13), 322 (75), 321 (8), 320 (41), 319 (15), 318 (17), 267 (21), 266 (19), 265 (100), 264 (11), 263 (57), 262 (20), 261 (24), 186 (11), 129 (39), 128 (17), 121 (23), 56 (20); NMR ($CDCl_3$) δ 0.83 (3 H, t, J = 7 Hz), 1.4 (4 H, m), 2.5 (t, 2 H, J = 7 Hz), 4.1 (5 H, s), 4.1 (2 H, t, J = 2 Hz), 4.2 (2 H, t, J = 2 Hz); ir (CCl_4, 0.1 cm ir tran) 3185 m, 2950 s, 2920 s, 2860 m, 1760 vw, 1725 vw, 1590 vw, 1460 m, 1410 w, 1385 w, 1255 m, 1195 w, 1150 m, 1100 m, 1020 s, and 1000 cm^{-1} m.

Anal. Calcd for $C_{14}H_{17}FeSe$: C, 52.33; H, 5.61. Found: C, 52.28; H, 5.58.

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Registry No.—I, 58463-77-7; II, 58463-78-8; VI, 58463-79-9; ferrocenyl selenocyanate, 58463-80-2; chloromercuriferrocene, 1273-75-2.

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Uvaretin, a New Antitumor Agent from *Uvaria acuminata* (Annonaceae)

Jack R. Cole,* Sterling J. Torrance, and Richard M. Wiedhopf

College of Pharmacy, University of Arizona, Tucson, Arizona 85721

Satish K. Arora and Robert B. Bates

Department of Chemistry, University of Arizona, Tucson, Arizona 85721

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The chloroform extract of *Uvaria acuminata* Oliv. has shown inhibitory activity against the P-388 lymphocytic leukemia test system of the National Cancer Institute. The major constituent of this extract was identified as the new 3′-benzyldihydrochalcone uvaretin, 1-[2,4-dihydroxy-3-(2-hydroxybenzyl)-6-methoxyphenyl]-3-phenyl-1-propanone ($C_{23}H_{22}O_5$). The structure was proven by x-ray crystallography and other methods.

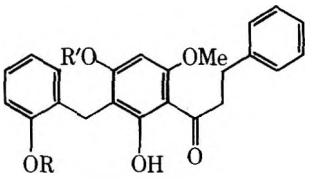
As a result of the continuing search for plants having tumor-inhibiting constituents, the chloroform extract of the roots of *Uvaria acuminata* Oliv. (Annonaceae)[17] was found to have inhibitory activity toward the P-388 (3PS) lymphocytic leukemia test system.

Discussion

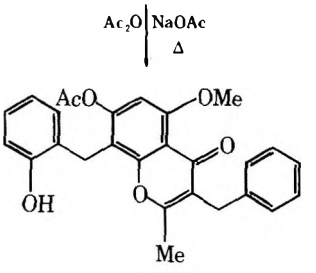
The major constituent of the chloroform extract of *Uvaria acuminata* Oliv. was found to be uvaretin, $C_{23}H_{22}O_5$. Uvaretin, subsequently shown to be I, was found to undergo the Kostanecki reaction[1] to give a 3-benzyl-2-methylchromone (II) characteristic of 2′-hydroxydihydrochalcones (e.g., phloretin).[2] In addition, the ^1H NMR spectrum of uvaretin shows the two 2-proton signals of an A_2B_2 pattern, centered at 2.90 and 3.33 ppm, expected for a β-propiophenone moiety. This ^1H NMR spectrum also contains a signal (13.9 ppm) for an intramolecularly hydrogen-bonded phenolic hydroxyl group.

Uvaretin (I) forms a monomethyl ether (III) with diazomethane and a dimethyl ether (IV) with dimethyl sulfate, both of which still contain the internally bonded phenolic hydroxyl group.

Uvaretin (I) demonstrated an activity of 133% test/control (T/C) at 10 mg/kg in the 3PS system. The monomethyl ether (III) of uvaretin showed an activity of 132% T/C at 1 mg/kg



I, R = R′ = H
III, R = H; R′ = Me
IV, R = R′ = Me



II

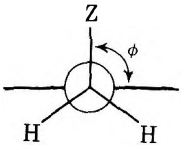
and the dimethyl ether (IV) demonstrated 144 and 141% T/C at 4 and 2 mg/kg, respectively. Activity in the 3PS system is defined as an increase in the survival of treated animals over that of controls resulting in a T/C $\geq$ 125%.[3]

Table I. Fractional Coordinates and Estimated Standard Deviations

Atom	x/a	y/b	z/c
O1	−0.2725 (2)	0.2168 (4)	0.3601 (2)
O2	−0.4210 (2)	0.1098 (4)	0.2912 (2)
O3	−0.5740 (2)	0.1910 (4)	−0.0145 (2)
O4	−0.2845 (2)	0.4043 (4)	0.1179 (2)
O5	−0.5681 (2)	0.1921 (4)	0.3197 (2)
C1	−0.0252 (3)	0.3633 (7)	0.3716 (3)
C2	0.0270 (3)	0.2417 (8)	0.3475 (3)
C3	0.1053 (4)	0.2995 (9)	0.3432 (4)
C4	0.1337 (3)	0.4675 (9)	0.3614 (4)
C5	0.0838 (4)	0.5832 (9)	0.3849 (4)
C6	0.0052 (3)	0.5290 (8)	0.3890 (3)
C7	−0.1111 (3)	0.3110 (7)	0.3776 (3)
C8	−0.1845 (3)	0.3360 (6)	0.2877 (3)
C9	−0.2698 (2)	0.2680 (5)	0.2871 (2)
C10	−0.2825 (3)	0.4505 (7)	0.0329 (3)
C1′	−0.3479 (2)	0.2579 (5)	0.2069 (2)
C2′	−0.4229 (2)	0.1730 (5)	0.2112 (2)
C3′	−0.4986 (2)	0.1494 (5)	0.1388 (2)
C4′	−0.5002 (2)	0.2137 (5)	0.0576 (2)
C5′	−0.4295 (2)	0.3000 (5)	0.0487 (2)
C6′	−0.3548 (2)	0.3206 (5)	0.1223 (2)
C7′	−0.5734 (3)	0.0461 (5)	0.1472 (2)
C1″	−0.6459 (2)	0.1494 (5)	0.1609 (2)
C2″	−0.6409 (2)	0.2125 (5)	0.2438 (2)
C3″	−0.7099 (2)	0.2988 (6)	0.2544 (2)
C4″	−0.7863 (3)	0.3238 (6)	0.1815 (3)
C5″	−0.7929 (3)	0.2620 (7)	0.0985 (3)
C6″	−0.7233 (3)	0.1751 (6)	0.0895 (3)
HC2	0.009 (2)	0.119 (5)	0.334 (2)
HC3	0.140 (2)	0.217 (5)	0.317 (2)
HC4	0.197 (2)	0.521 (5)	0.363 (2)
HC5	0.101 (2)	0.714 (5)	0.400 (2)
HC6	−0.026 (2)	0.613 (5)	0.408 (2)
H1C7	−0.124 (2)	0.380 (5)	0.430 (2)
H2C7	−0.103 (2)	0.191 (5)	0.403 (2)
H1C8	−0.167 (2)	0.285 (5)	0.240 (2)
H2C8	−0.188 (2)	0.454 (5)	0.270 (2)
H1C10	−0.295 (3)	0.336 (6)	−0.005 (3)
H2C10	−0.336 (3)	0.518 (6)	−0.003 (3)
H3C10	−0.226 (3)	0.506 (6)	0.043 (3)
HC5′	−0.434 (2)	0.341 (5)	−0.014 (2)
H1C7′	−0.547 (2)	−0.034 (5)	0.195 (2)
H2C7′	−0.603 (2)	−0.033 (5)	0.088 (2)
HC3″	−0.702 (2)	0.335 (5)	0.318 (2)
HC4″	−0.836 (2)	0.377 (5)	0.192 (2)
HC5″	−0.849 (2)	0.281 (5)	0.044 (2)
HC6″	−0.726 (2)	0.131 (5)	0.029 (2)
HO2	−0.365 (2)	0.146 (5)	0.339 (2)
HO3	−0.564 (2)	0.226 (5)	−0.063 (2)
HO4	−0.519 (2)	0.159 (5)	0.308 (2)

The structure of uvaretin was determined to be I by x-ray crystallography. Fractional coordinates are given in Table I, and bond distances and angles in Figure 1. The average estimated standard deviations for C–C, C=O, C–O distances are 0.006, 0.005, and 0.005 Å, respectively, and for angles, 0.3°. The weighted average of C–C bond lengths in aromatic rings (C1–C6, C1′–C6′, C1″–C6″) are 1.383 ± 0.006, 1.394 ± 0.006, and 1.387 ± 0.006 Å, which differ slightly from the value 1.393 Å observed in crystalline benzene.[4] The average internal angle in the benzene rings is 120.0°. The distances between oxygens partaking in intramolecular hydrogen bonds (dashed lines) are 2.441 (O1–O2) and 2.703 (O2–O5) Å. The C–C–C angles about tetrahedral carbons C7 and C8 are slightly larger than the tetrahedral angle, while that about C7′ is enlarged to 116.4°.[5]

The molecular conformation is shown in Figure 2.[6] It is partially governed by the intramolecular hydrogen bonds shown as dashed lines; e.g., the torsion angle O1–C9–C1′–C2′ is 6.7°. The C1′–C9–C8–C7 angle is 172.2°, C9–C8–C7–C1 is 173.8°, and C10–O4–C6′–C5′ is 9.3°.[7] The remaining three carbon–carbon single bonds are of the type Aryl–CH_2Z; the two of these influenced by the O2–O5 hydrogen bond have torsion angles ϕ of 81.5 (C2″–C1″–C7′–C3′) and 87.2° (C1′–



C7′–C3′–C4′), and the third ϕ is 89.1° (C8–C7–C1–C2). In these three cases ϕ is 80–90°, but this is not generally true, since in kavain it is 18.5°,[8] in dihydrokavain 6.5°,[9] in dibenzyl 71.6°,[10] and in 4,4′-dimethyldibenzyl 72.6°.[11]

The molecular packing, shown in Figure 3, is partially controlled by the intermolecular hydrogen bond between O3 and O5 (2.845 Å, dotted line). These bonds create infinite chains of molecules in the *c* direction. Other intermolecular distances less than 3.5 Å are O1–C10 (3.118 Å), O2–C2″ (3.345 Å), O5–C6′ (3.401 Å), and O2–C3″ (3.480 Å).

Experimental Section[19]

Extraction Procedure. The roots (dried and ground, 1.58 kg) of *Uvaria acuminata* were extracted exhaustively in a Lloyd-type extractor with petroleum ether (bp 30–60 °C). After removal of the solvent, the petroleum ether extraction residue weighed 4.8 g. The marc was then extracted in a like fashion with ethanol. The solvent from the ethanol extract was removed in air to provide 42.7 g of residue. The latter was partitioned between chloroform and water (1:1) and, after the layers had been separated, the chloroform was removed in air and the water lyophilized. The former yielded 22.8 g of residue and the latter 20.0 g.

Isolation of Uvaretin (I). The residue from the chloroform phase (above, 6.3 g) was chromatographed over silica gel 60 (900 g, 40 × 1800 mm), eluting with dichloromethane, benzene, and ethyl acetate, 3:6:1, respectively. Those fractions containing the major component based upon thin layer chromatography were combined to yield 2.24 g of an oily material, largely uvaretin. Solidification was effected with carbon tetrachloride/acetone giving 0.9 g of purified uvaretin. Recrystallization from acetonitrile gave pure material as colorless platelets, mp 162–163 °C. The infrared [(KBr) 3300, 1625, and 1590 cm^{-1}], ultraviolet [(EtOH) λ_{max} 330 nm (log ϵ 4.48), 284 (sh) (4.11), and 254 (sh) (3.82)], ^1H NMR [(acetone-d_6) δ 2.90 and 3.33 (each 2 H, A_2B_2 pattern), 3.83 (3 H, s), 4.25 (2 H, s), 6.20 (1 H, s), 6.9 (4 H, m), 7.23 (5 H, s), 8.8 (2 H, br), and 13.9 (1 H, s)], and mass [*m/e* 378 (M^+ base), 273, 246, 179, 167, 140, 107, and 91] spectra were in accord with structure I.

Anal. Calcd for $C_{23}H_{22}O_5$: C, 73.00; H, 5.85. Found: C, 72.90; H, 5.88.

Kostanecki Reaction Product II. Uvaretin (100 mg) was treated with fused sodium acetate (0.2 g) and acetic anhydride (2 ml) under the usual Kostanecki conditions.[12] Following workup, the crude oily product (100 mg) was passed through an alumina (activity grade II) column and crystallized from ethyl acetate. Two recrystallizations from ethyl acetate/methanol gave pure material (22 mg) as colorless, tiny cubes, mp 256–259 °C. The alumina treatment appears to have removed the acetate moiety from C-2″. The infrared [(KBr) 3070, 1760, 1640, 1560, and 1200 cm^{-1}], ultraviolet [(EtOH) λ_{max} 312 nm (log ϵ 3.75), 295 (3.77), 262 (4.30), 253 (3.27), and 237 (3.34)], ^1H NMR [(pyridine-d_5) δ 2.10 (3 H, s), 2.33 (3 H, s), 3.72 (3 H, s), 3.90 (2 H, s), 4.31 (2 H, s), 6.66 (1 H, s), 7.0 (4 H, m), and 7.2 (5 H, s)], and mass [*m/e* 444 (M^+), 402, 384, 207, 149, 129, 128, 107, and 91 (base)] spectra were in accord with structure II.

Anal. Calcd for $C_{27}H_{24}O_6 \cdot H_2O$: C, 70.11; H, 5.66. Found: C, 70.24; H, 5.39.

Uvaretin Monomethyl Ether (III). Uvaretin (110 mg) in dry dioxane (20 ml) was treated in the usual manner[13] with diazomethane, generated from *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (Aldrich, 1 g). After 2 h reaction at room temperature, workup afforded 100 mg of uvaretin monomethyl ether, which was recrystallized from ethyl acetate to colorless platelets, mp 138–139 °C. Uvaretin monomethyl ether prepared in this way had infrared [($CHCl_3$) 3380, 1610, and 1590 cm^{-1}], ultraviolet [(EtOH) λ_{max} 290 nm (log ϵ 4.40)], ^1H NMR [(acetone-d_6) δ 3.0 and 3.3 (each 2 H, A_2B_2 pattern), 3.90 (8 H, s), 6.26 (1

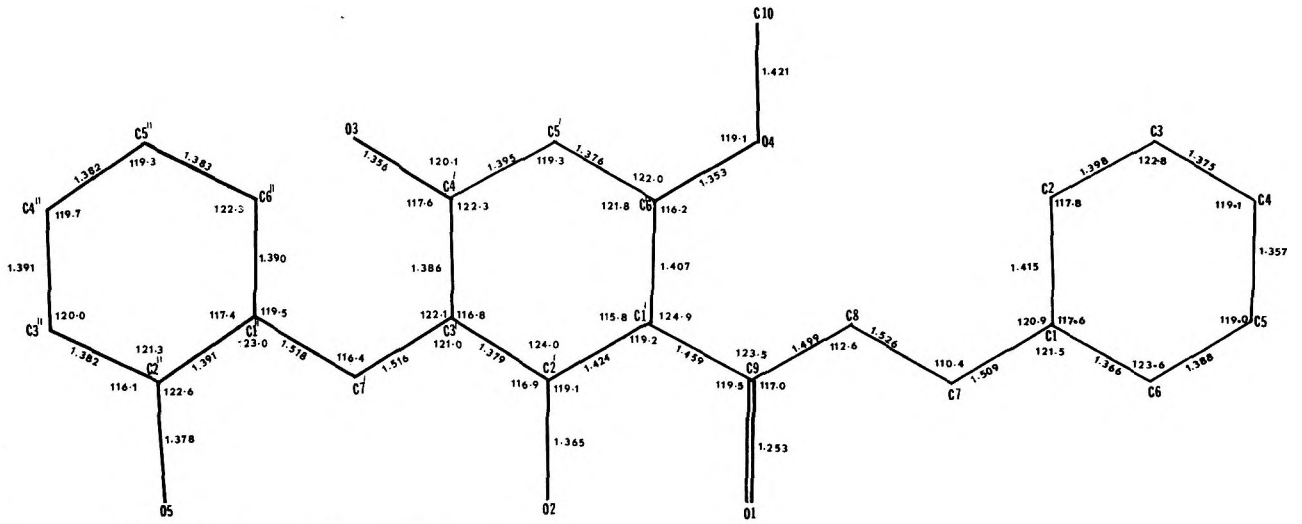


Figure 1. Bond lengths (Å) and angles (deg) in uvaretin (I).

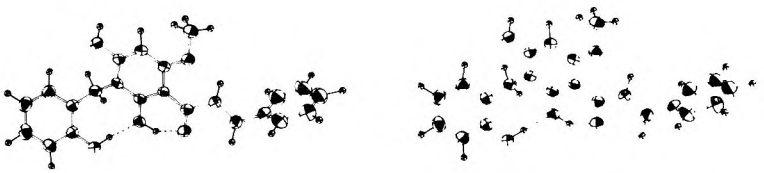


Figure 2. Stereoscopic view of uvaretin (I). Hydrogen atoms are shown as spheres and other atoms as 50% probability ellipsoids.

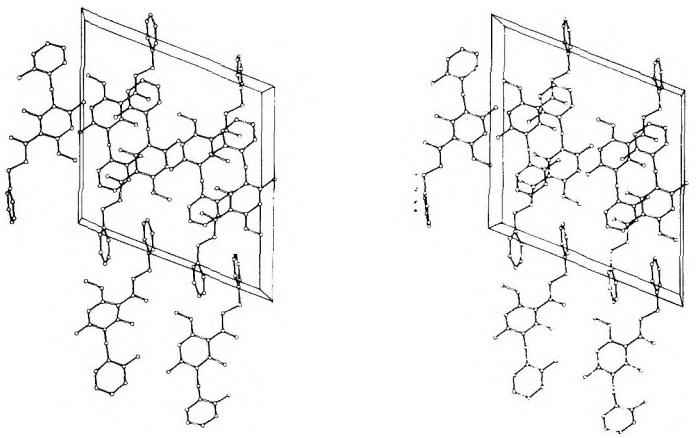


Figure 3. Stereoscopic view of a unit cell, *b* axis projection, with the *a* axis vertical.

H, s), 6.9 (4 H, m), 7.20 (5 H, s), 7.9 (1 H, br), and 14.5 (1 H, s)], and mass [*m/e* 392 (M^+), 287, 260, 193, 181, 154, 107, 91 (base), and 87] spectra in accord with structure III.

Anal. Calcd for $C_{24}H_{24}O_5$: C, 73.45; H, 6.16. Found: C, 73.07; H, 6.27.

Uvaretin Dimethyl Ether (IV). Uvaretin (200 mg) was methylated with sodium hydroxide (0.5 g) and dimethyl sulfate (1.2 g) in the usual way.[14] After workup, the crude semisolid product (170 mg) was recrystallized twice from hexane/benzene to provide pure material as colorless, tiny needles, mp 122–123 °C. The uvaretin dimethyl ether prepared in this way had infrared [($CHCl_3$) 3400, 1610, and 1590 cm^{-1}], ultraviolet [(EtOH) λ_{max} 291 nm (log ϵ 4.40)], ^1H NMR [($CDCl_3$) 3.0 and 3.3 (each 2 H, A_2B_2 pattern), 3.75 (3 H, s), 3.81 (6 H, s), 3.91 (2 H, s), 5.96 (1 H, s), 6.8 (4 H, m), 7.20 (5 H, s), and 13.9 (1 H, s)], and mass [*m/e* 406 (M^+), 301, 274, 193, 181, 166, 121 (base), 91, 77, and 65] spectra in accord with structure IV.

Anal. Calcd for $C_{25}H_{26}O_5$: C, 73.87; H, 6.44. Found: C, 74.27; H, 6.44.

Crystallographic Study of Uvaretin (I). Colorless crystals were grown from chloroform/benzene. A needle 0.2 × 0.2 × 0.4 mm was mounted with the *b* axis parallel to the goniostat ϕ axis. The space group was determined by film methods to be $P2_1/c$. The cell parameters were found using eight reflections on a Picker-FACS-I diffractometer (Cu Kα, λ = 1.54178 Å, graphite monochromator) to be a = 16.499 (6), b = 7.723 (2), c = 16.055 (6) Å, and β = 111.11° (1). The crystal density was measured by flotation as 1.316 g/ml, agreeing well with a calculated density of 1.317 g/ml assuming four molecules in the unit cell. Intensity data were collected up to 2θ = 120° using a scintillation counter with pulse-height analyzer, θ–2θ scan technique, 2°/min scan rate, 10-s background counts, attenuators when the count rate exceeded 10^4 counts/s, and 2° scan range with a dispersion factor allowing for α_1–α_2 splitting at large 2θ values. Of 2676 independent reflections measured, 2343 > 3σ(I) were considered observed. Three standard reflections were monitored every 50 measurements to check the crystal alignment and the stability; no decrease in the intensity of standards was observed. Lorentz and polarization corrections were applied to the data, but no correction was made for absorption.

Phases for reflections with normalized structure factor $E > 1.5$ were generated using the direct method program of Long.[15] Although normally the solution with highest consistency index and least number of cycles is correct, in the present case the correct solution was third highest in consistency index and second lowest in number of cycles. All nonhydrogen atoms were located on an E map using calculated phases as coefficients. Full matrix least-squares refinement in which positional and isotropic thermal parameters were varied reduced R to 0.122. Two more cycles of least-squares refinement using anisotropic thermal parameters reduced R to 0.087. A difference map at this stage revealed all the hydrogen atoms. One more cycle of least-squares refinement using anisotropic temperature factors for nonhydrogen atoms and isotropic temperature factors (of nonhydrogen atoms to which they were attached) for hydrogen atoms reduced R to 0.060. The refinement was terminated at this stage since

the ratios of shifts in parameters to estimated standard deviations were all less than 0.2. The refinement was based on F_o, the quantity minimized being $\Sigma w(F_o - F_c)^2$. Unit weights were used. The scattering factors used were those of Hanson, Herman, Lea, and Skillman.[16]

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Registry No.—I, 58449-06-2; II, 58449-07-3; III, 58449-08-4; IV, 58449-09-5.

Supplementary Material Available. Tables of temperature factors and bond distances and angles involving hydrogens (3 pages). Ordering information is given on any current masthead page.

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(18) Of the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Bethesda, Md.
(19) Carbon and hydrogen analyses were performed by Chemalytics, Inc., Tempe, Ariz. ^{1}H NMR, ir, uv, and mass spectra were determined using a Varian T-60 spectrometer, a Beckman IR-33, a Beckman DBG, and a Hitachi Perkin-Elmer double focusing spectrometer (Model RMU-6-E), respectively. The melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

Antitumor Agents from *Jatropha macrorhiza* (Euphorbiaceae). II. Isolation and Characterization of Jatrophatrione[1]

Sterling J. Torrance, Richard M. Wiedhopf, and Jack R. Cole*

College of Pharmacy, University of Arizona, Tucson, Arizona 85721

Satish K. Arora, Robert B. Bates, William A. Beavers, and Robert S. Cutler

Department of Chemistry, University of Arizona, Tucson, Arizona 85721

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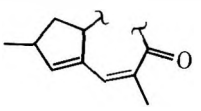
As a result of the continuing search for plants having tumor-inhibiting constituents, the chloroform extract of the roots of *Jatropha macrorhiza* Benth. (Euphorbiaceae)[2] was found to possess inhibitory activity toward the P-388 (3PS) lymphocytic leukemia test system.

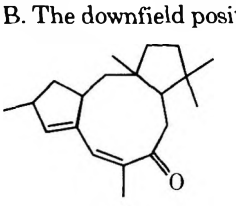
Discussion

One constituent of the chloroform extract of *Jatropha macrorhiza* Benth. roots is the new diterpene jatrophatrione, $C_{20}H_{26}O_3$, subsequently shown to be I. The initial spectral data (ir, uv, ^{1}H NMR) of jatrophatrione immediately led to the conclusion that jatrophatrione was structurally related to jatrophone (II, $C_{20}H_{24}O_3$), previously isolated from *Jatropha gossypiifolia*.[4] Specifically, the partial structure A appeared to be a common feature of the two diterpenes. Table I shows the nearly identical spectral data for jatrophatrione (I) and jatrophone (II) generated by partial structure A.



A

Assuming a close biogenetic and structural relationship to jatrophone (II), the rest of the constitution of jatrophatrione (I) was deduced. The two double bonds in partial structure A accounted for all of the vinylic carbon atoms (^{13}C NMR), and with two more carbonyl groups (ir, ^{13}C NMR) there had to be one more ring. That the latter is five membered could be seen in the infrared spectrum at 1746 cm^{-1} (cyclopentanone) and a quaternary methyl group in the ^{1}H NMR spectrum (δ 1.47) dictated that the closure of this ring be as shown in partial structure B. The downfield position of this angular



B

methyl group suggested that it is flanked by both remaining carbonyl groups, as in structure I. Scheme I shows how the tricyclic structures I (jatrophatrione) and II (jatrophone) may be derived in nature from bicyclic precursor III; steps to this precursor from geranylgeranyl pyrophosphate via casbene oxidation product IV are readily imagined (cf. ref 5).

An x-ray study on jatrophatrione (I) confirmed the proposed constitution and showed the relative configurations to be as depicted. The absolute configuration was not determined crystallographically but is based on the assumption that jatrophatrione (I) and jatrophone (II) possess the same configuration at C2.[4] Bond distances are given in Table II and bond angles in Table III.

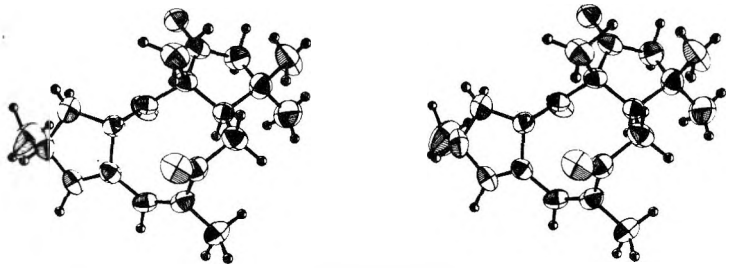


Figure 1. Stereoscopic view of jatrophatrione (I).

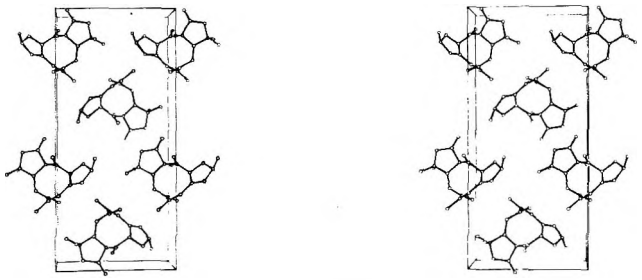
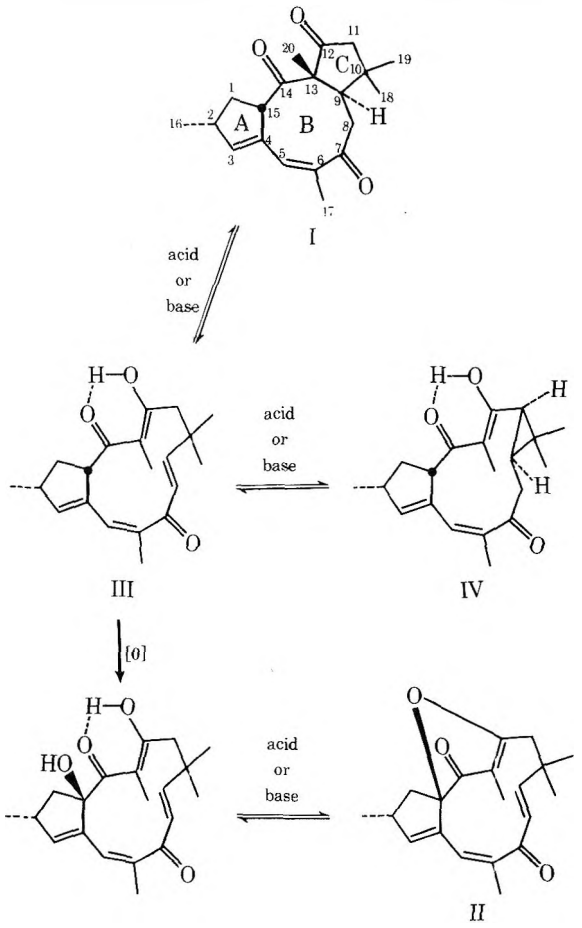


Figure 2. Stereoscopic view of a unit cell, *a* axis projection, with the *c* axis vertical and the *b* axis horizontal.

Scheme I. Possible Biological Route to Jatrophatrione (I) and Jatrophone (II) from Bicyclic Precursor III



The molecular conformation is depicted in Figure 1. The most striking feature is the lack of conjugation between the diene system and the C7–O3 carbonyl group: torsion angle C5–C6–C7–O3 is 61.0°. Apparently nonbonded steric interactions and angle strain cause conformations which would provide better overlap between these π systems to be of higher energy. A similar torsion angle is observed between the corresponding groups in jatrophone (II).[6] The conjugated diene system in I is approximately transoid with a twist of 15.5° from coplanarity, based on the C3–C4–C5–C6 torsion angle. Torsion angles around the rings (Table IV) show a nearly planar A ring, an irregularly puckered B ring, and an envelope conformation[7] with C10 at the point for the C ring. Figure 2 shows the molecular packing in the crystal.

Table I. A Comparison of Some Spectral Data for Jatrophatrione and Jatrophone

	Jatrophatrione	Jatrophone
Ir	1690 cm^{-1}	1690 cm^{-1}
Uv	280 nm	285 nm
^1H NMR	Vinyl protons δ 5.82, 6.08	δ 5.86, 6.04
	Vinyl methyl δ 1.93	δ 1.83

Table II. Intramolecular Bond Distances, with Estimated Standard Deviations in Parentheses

Bond	Distance, Å
O1–C14	1.200 (6)
O2–C12	1.200 (7)
O3–C7	1.226 (7)
C1–C2	1.499 (9)
C1–C15	1.557 (7)
C2–C3	1.476 (8)
C2–C16	1.547 (11)
C3–C4	1.319 (7)
C4–C5	1.474 (7)
C4–C15	1.524 (7)
C5–C6	1.327 (8)
C6–C7	1.503 (9)
C6–C17	1.510 (8)
C7–C8	1.504 (8)
C8–C9	1.514 (7)
C9–C10	1.563 (8)
C9–C13	1.560 (7)
C10–C11	1.529 (8)
C10–C18	1.496 (10)
C10–C19	1.541 (11)
C11–C12	1.460 (8)
C12–C13	1.535 (8)
C13–C14	1.540 (8)
C13–C20	1.564 (8)
C14–C15	1.523 (7)

Jatrophatrione (I) demonstrated activities of 130% test/control (T/C) and 141% T/C at 1 and 0.5 mg/kg, respectively, in the 3PS system. Activity in the 3PS is defined as an increase in the survival of treated animals over that of controls resulting in a T/C $\geq$ 125%.[8]

Jatrophatrione (I) is thus active, even though it lacks the C8–C9 double bond to which thiols add nucleophilically in jatrophone (II).[9] An alternative conjugate addition at C3 or C5 is rendered unlikely in view of the lack of conjugation between the diene system and the attached carbonyl group (see above); indeed, under conditions under which *n*-propyl mercaptan adds in good yield to the C8–C9 double bond of jatrophone (II),[9] *n*-butyl mercaptan does not react appreciably with jatrophatrione (I). Possibly the activity of I is due to its ability to undergo reverse Michael addition to give III, which can undergo addition similar to that of II.

Experimental Section[3]

Extraction Procedure. The fresh ground roots (200 lb) of *Jatropha macrorhiza* were extracted exhaustively in a Lloyd-type extractor with ethanol. The solvent from the ethanol extract was removed in air and the residue partitioned between chloroform and water (1:1). After the layers had been separated, the chloroform was removed in air and this resulted in 130.3 g of residue.

Isolation of Jatrophatrione (I). The residue from the chloroform phase (above, 100 g) was stirred vigorously with ether (1.4 l.) and filtered. This provided 7 g of ether-insoluble residue, and after removal of the solvent in vacuo, 92 g of ether-soluble material. The ether-soluble fraction (50 g) was then chromatographed over silica gel 60 (E. Merck, 850 g, 55 × 840 mm). Elution of the column was begun with benzene and continued with increasing amounts of chloroform in

Table III. Bond Angles with Estimated Standard Deviations in Parentheses

Atoms	Angle, deg
C2–C1–C15	108.3 (5)
C1–C2–C3	104.2 (5)
C1–C2–C16	113.9 (5)
C3–C2–C16	112.7 (5)
C2–C3–C4	113.6 (4)
C3–C4–C5	124.0 (4)
C3–C4–C15	111.8 (4)
C5–C4–C15	124.0 (4)
C4–C5–C6	130.6 (4)
C5–C6–C7	123.1 (5)
C5–C6–C17	122.5 (4)
C7–C6–C17	114.3 (4)
C6–C7–C8	118.1 (5)
C6–C7–O3	119.6 (4)
C8–C7–O3	122.4 (4)
C7–C8–C9	111.8 (4)
C8–C9–C10	114.9 (4)
C8–C9–C13	116.5 (4)
C10–C9–C13	105.5 (4)
C9–C10–C11	101.9 (5)
C9–C10–C18	109.9 (5)
C9–C10–C19	113.1 (5)
C11–C10–C18	112.5 (6)
C11–C10–C19	111.7 (5)
C10–C11–C12	106.9 (5)
C11–C12–C13	110.0 (4)
C11–C12–O2	128.3 (5)
C13–C12–O2	121.7 (4)
C12–C13–C14	109.1 (4)
C12–C13–C20	106.7 (4)
C14–C13–C20	110.3 (4)
C12–C13–C9	103.5 (4)
C14–C13–C9	109.0 (4)
C20–C13–C9	117.7 (4)
C13–C14–C15	121.4 (4)
C13–C14–O1	118.2 (4)
C15–C14–O1	120.3 (4)
C14–C15–C1	110.5 (4)
C14–C15–C4	111.6 (4)
C1–C15–C4	101.6 (4)

Table IV. Torsion Angles in the Rings of Jatrophatrione (I)

	Atoms	Angle, deg
	C1–C2–C3–C4	5.3
	C2–C3–C4–C15	−1.7
Ring A	C3–C4–C15–C1	−2.4
	C4–C15–C1–C2	5.5
	C15–C1–C2–C3	−6.5
	C4–C5–C6–C7	9.5
	C5–C6–C7–C8	−120.8
	C6–C7–C8–C9	61.2
	C7–C8–C9–C13	62.0
Ring B	C8–C9–C13–C14	−93.6
	C9–C13–C14–C15	96.0
	C13–C14–C15–C4	−121.1
	C14–C15–C4–C5	54.7
	C15–C4–C5–C6	21.2
	C9–C10–C11–C12	33.6
	C10–C11–C12–C13	−21.1
Ring C	C11–C12–C13–C9	−0.7
	C12–C13–C9–C10	21.6
	C13–C9–C10–C11	−33.7

benzene. Elution with 100% chloroform produced a semicrystalline fraction (7.0 g) which was recrystallized from ether–hexane. This gave jatrophatrione (I, 450 mg) and another recrystallization resulted in pure material as colorless spears, mp 148–150 °C (starts to sweat at 137 °C). Jatrophatrione (I) is optically active, $[\alpha]^{25}D$ −187° (*c* 0.2, $CHCl_3$). The infrared [($CHCl_3$) 1746, 1690, 1640, and 1632 cm^{-1}], ultraviolet [(EtOH), λ_{max} 280 (log ϵ 3.49), 244 (shoulder, 3.95), and 223 nm (4.04)], ^1H NMR [($CDCl_3$) δ 0.91 (3 H, s), 1.11 (3 H, d, J = 7 Hz), 1.23 (3 H, s), 1.47 (3 H, s), 1.93 (3 H, br s), 2.2–3.0 (8 H, complex), 4.08 (1 H, br t, J = 7 Hz), 5.82 (1 H, m), and 6.08 (1 H, m)], ^{13}C NMR [($CDCl_3$) δ 13.0 (q), 19.2 (2 carbons, both q), 21.6 (q), 25.6 (q), 34.1 (t), 34.5 (t), 35.2 (s), 36.6 (d), 46.8 (d), 47.2 (d), 51.0 (t), 59.1 (s), 116.7 (d) 124.5 (s), 126.8 (s), 131.8 (d), 193.8 (s), 196.2 (s) and 198.8 (s)], and mass [*m/e* 314 (M^+), 286, 256, 162 (base), 147, 120, 105, 91, 79, 69, and 55] spectra were in complete agreement with structure I.

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.33. Found: C, 76.49; H, 8.53.

Crystallographic Study of Jatrophatrione (I). Colorless crystals of I were grown from ether–petroleum ether. A needle 0.1 × 0.2 × 1.2 mm was mounted with the *a* axis parallel to the goniostat ϕ axis. The space group was found to be $P2_12_12_1$ by a combination of film and counter methods. The cell lengths were found using nine reflections on a Picker FACS-I diffractometer (Cu Kα, λ = 1.54178 Å, graphite monochromator) to be a = 6.731 (2), b = 11.149 (4), c = 24.188 (9) Å. The crystal density was measured by flotation in aqueous KI as 1.13 g/ml, in agreement with a calculated density of 1.15 g/ml assuming four molecules in the unit cell. Intensity data were collected using a scintillation counter with pulse-height analyzer, θ–2θ scan technique, 2°/min scan rate, 10-s background counts, attenuators when the count rate exceeded 10^4 counts/s, and 2° scan range with a dispersion factor allowing for α_1–α_2 splitting at large 2θ values. Of 1644 independent reflections measured, 1267 > 3σ(I) were considered observed. No decrease in intensity of standard reflections was observed, and no correction was made for absorption.

The structure was solved using MULTAN.[10] All nonhydrogen atoms were located on the first E map. Full-matrix least-squares refinement with isotropic thermal parameters reduced $R = [\Sigma w(F_o - |F_c|)^2/\Sigma wF_o^2]^{1/2}$ to 0.128, and with anisotropic, to 0.096. A difference map revealed all of the hydrogen positions. Further refinement using anisotropic temperature factors for nonhydrogen atoms and isotropic temperature factors (of nonhydrogen atoms to which they were attached) for hydrogens reduced R to its final value of 0.048. Refinement was based on F_o, the quantity minimized being $\Sigma w(F_o - |F_c|)^2$, with unit weights. The scattering factors used were those of Hanson, Herman, Lea, and Skillman.[11]

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Registry No.—I, 58298-76-3.

Supplementary Material Available. Tables of atomic coordinates and temperature factors (3 pages). Ordering information is given on any current masthead page.

References and Notes

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(2) Identification was confirmed by R. M. Wiedhopf, College of Pharmacy, and Dr. Charles T. Mason, Botany Department, University of Arizona, Tucson, Ariz. A reference specimen was deposited in the University of Arizona Herbarium.
(3) Carbon and hydrogen analyses were performed by Chemalytics, Inc., Tempe, Ariz. Mass, ^{13}C NMR, ^1H NMR, uv, and ir spectra were recorded using a Hitachi Perkin-Elmer double focusing spectrometer (Model RMU-6E), a Bruker WH-90 (22.6 MHz) spectrometer, a Varian T-60 spectrometer, a Beckman DB-G spectrophotometer, and a Beckman IR-33, respectively. The optical rotation was obtained on a Rudolph Model 70 polarimeter and melting points were determined on a Kofler hot-stage apparatus and are uncorrected.
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Sparsomycin, Structure and Chemistry[1]

Paul F. Wiley* and Forrest A. MacKellar

Research Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001

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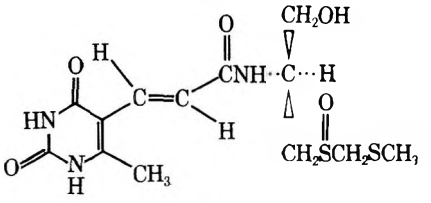
A combination of spectral data and chemical degradation has established the structure of sparsomycin to be that shown in 1.

The isolation of the antibiotic sparsomycin (1) was reported some years ago by Argoudelis and Herr,[2] and a preliminary report discussing its structure has also been published.[3] The present publication presents in detail the evi-



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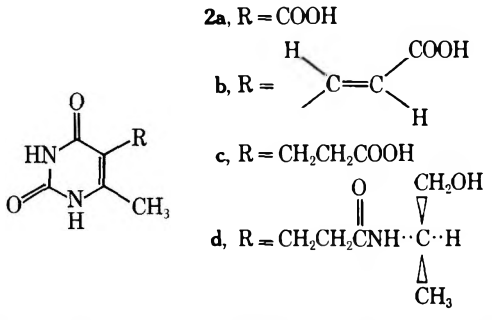
dence for the previously proposed structure (1) and discusses further the chemistry of sparsomycin.

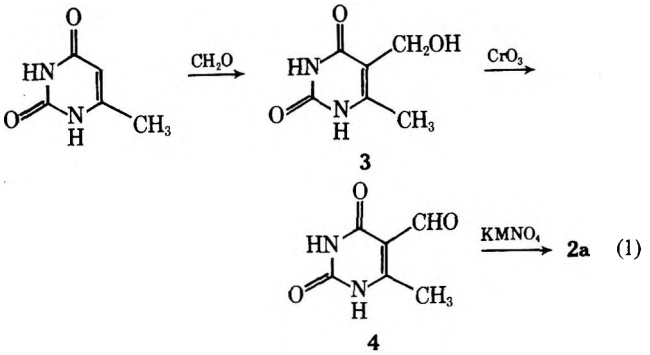
The molecular formula for 1 suggested by Argoudelis and Herr was $C_{13}H_{19-21}N_3O_6S_2$. This suggestion was based on analytical data on material which was subsequently found to be a hydrate. Sparsomycin dried under high vacuum at room temperature for 48 h or more loses 80–90% of its water content. Analyses done on material dried in this way correspond to the molecular formula $C_{13}H_{19}N_3O_5S_2$. The presence of two CH_3C groups was reported, again based on analysis, and acetyl and methoxyl groups were found to be absent. However, subsequent analyses showed the presence of only one CH_3C group although the NMR spectrum of sparsomycin showed the presence of a second methyl group. Titration indicated the presence of a weakly acidic proton.

Oxidation of sparsomycin with aqueous potassium permanganate led to only one product (**2a**) which was an acid having a molecular formula, shown by analysis and mass spectrometry, of $C_6H_6N_2O_4$. The composition and the uv



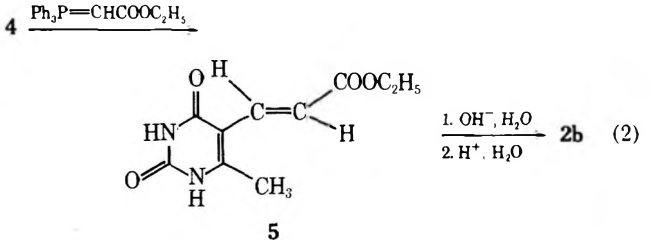
spectrum, which had a single strong maximum at 267 nm shifting to 288 nm with base, suggested a substituted uracil. Indications of the presence of a carboxyl group in the product by its solubility in weak base and the presence of a methyl group shown by its NMR spectrum first led to the view that the acid was 5-methylorotic acid. Such a consideration was also logical on biogenetic grounds. However, a direct comparison of **2a** with 5-methylorotic acid established that they differed. In such case the isomeric structure **2a** seemed the most likely one. Synthesis of **2a** by the route shown in eq 1 and comparison of the physical properties of the synthetic compound with those of the acid derived from sparsomycin showed that they were identical.

Mild acid hydrolysis of sparsomycin led to three products.



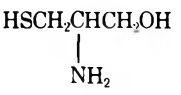
(1)

Cooling the reaction mixture gave a crystalline product (**2b**) having the molecular formula $C_8H_8N_2O_4$. Analytical data were consistent with such a formula, but the mass spectrum did not give a molecular ion of 196 as required but gave an *m/e* of 152. Since titration indicated the presence of a carboxyl group, **2b** was converted to a methyl ester which gave the mass spectrum molecular weight expected for the methyl ester of a $C_8H_8N_2O_4$ acid. The compound **2b** differs from **2a** by the elements of CH=CH, and its NMR spectrum has a doublet of doublets centered at δ 7.25 (J = 16 Hz) which would be indicative of a trans vinyl system. These data point to a structure represented by the expression **2b.** Synthesis of **2b** by the route shown in eq 2 and comparison of the product with that derived from



(2)

sparsomycin using various physical properties (TLC, ir, uv, NMR, etc.) showed that the two were the same. Alkaline hydrolysis of sparsomycin also formed **2b.** A second product of the acid hydrolysis was isolated only as its diacetyl derivative. Analyses and mass spectra indicated a molecular formula of $C_7H_{13}NSO_3$. Its NMR spectrum showed that it contained two acetyl groups, and the ir spectrum suggested the presence of an acetate and an acetyl derivative of a primary amine. The NMR spectrum of the acetyl derivative and subsequently discussed degradative studies suggested that the compound formed from sparsomycin contained a three-carbon chain with each carbon being substituted by one of the elements, nitrogen, oxygen, or sulfur. Cysteinol (6) would be such a compound. The triacetyl derivative of L-cysteinol was reported



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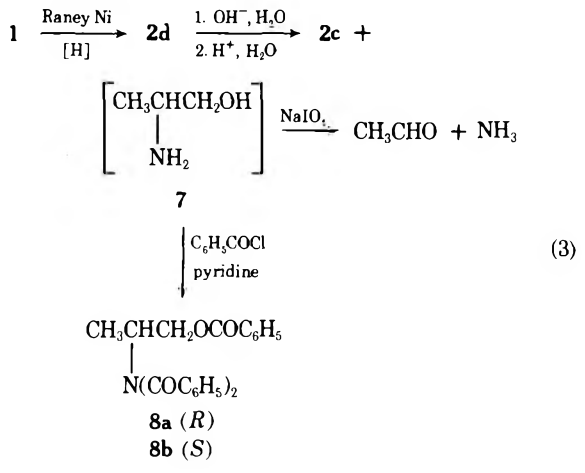
by Enz and Cecchinato[4] to have been prepared by reduction of cysteine ethyl ester followed by acetylation. If the product isolated from sparsomycin is a derivative of either D- or L-

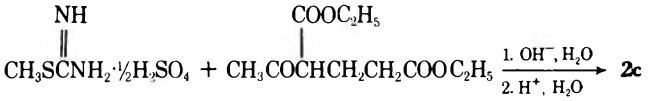
cysteinol, it would be expected to give a triacetyl derivative as was reported previously. However, as the only evidence presented by Enz and Cecchinato for triacetylation was analysis, and since their product gave the same melting point as the compound reported here, it may be that a diacetyl derivative was the one actually prepared previously. In any case it is probable that cysteinol is formed by acid hydrolysis of sparsomycin. The third product was formaldehyde which was identified as its 2,4-dinitrophenylhydrazone.

Treatment of sparsomycin with Raney nickel in boiling ethanol in order to bring about desulfurization gave two products, a gas and a solid (**2d**). The gaseous product was shown by its ir spectrum to be methane which was formed in the ratio of 2 mol to 1 mol of starting material. The high-resolution mass spectrum of the solid product indicated its molecular formula to be $C_{11}H_{17}N_3O_4$ although it was not obtained sufficiently pure to give good analytical values. Alkaline hydrolysis of **2d** followed by acidification formed an acid (**2c**) which had the molecular formula $C_8H_{10}N_2O_4$. In addition to **2c** the hydrolyzed material formed a second product which was isolated only as its tribenzoyl derivative (**8a**). That **8a** contained three benzoyl residues was shown by its mass spectrum. When the alkaline hydrolysate was neutralized followed by periodate oxidation, the products were acetaldehyde and ammonia (eq 3). The former was isolated and



identified as its 2,4-dinitrophenylhydrazone and the latter as its salt with *p*-hydroxyazobenzene-*p'*-sulfonic acid.

The fact that **2c** had the molecular formula of **2b** with two atoms of hydrogen added, and that it was isolated from a reaction involving the use of Raney nickel, suggested that **2c** was the compound resulting from reduction of the olefinic group in **2b.** That this was the case was established by the synthesis of **2c** using the procedure used by Johnson and Heyl[5] (eq 4) to synthesize 1,2,3,4-tetrahydro-6-methyl-2,4-dioxo-5-pyrimidineacetic acid and comparing the product derived from sparsomycin with the synthetic compound.



(4)

In view of the structure of **2c** it seemed probable that **8a** was a derivative of the compound which was oxidized by periodate to give acetaldehyde and ammonia. If it is assumed that hydrolysis of **2d** occurs in a straightforward fashion with addition of only one molecule of water to give the two products, then the compound formed in addition to **2c** would have the molecular formula C_3H_9NO. It would then be, since it is oxidized by periodate to give acetaldehyde and ammonia, either 2-aminopropanol or 2-hydroxypropylamine. Synthesis of the tribenzoyl derivative (**8b**) of (*S*)-2-aminopropanol gave a compound which was identical in most properties (melting point, ir, NMR, R_f in TLC) with **8a** but had a rotation of +63.2° as compared to −61.4° for **8a** in the same solvent. Consequently **8a** must be the tribenzoyl derivative of (*R*)-2-aminopropanol (**7**) which would be expected to react with periodate to give acetaldehyde and ammonia.

The isolation of **2b** by hydrolysis of sparsomycin suggests that **2b** is combined through its carboxyl group in an ester or amide linkage with a $C_5H_{12}NO_2S$ moiety. Since sparsomycin is not basic, the attachment must be through the amino nitrogen present in the (*R*)-2-aminopropanol formed as shown in eq 4. In such case the acid **2c** must be combined with (*R*)-2-aminopropanol as the structure indicated in the expression **2d.** The NMR spectrum of sparsomycin contains two singlet signals attributable to methyl groups. The CH_3C of **7** then cannot be present in sparsomycin as its NMR spectrum would have a doublet arising from a methyl group. This group then must be formed in the desulfurization, and the carbon atom of its methyl group must be attached to a sulfur atom which is part of a $C_2H_5S_2O$ moiety. The evolution of 2 mol of methane during desulfurization indicates that this moiety must have an –S–C–S–C arrangement with a terminal methyl. The NMR spectrum of sparsomycin has signals attributable to three methylene groups. One of these is a complex AB pattern (of an ABX) system with signals centered at δ 3.65 and must be the methylene of a hydroxymethyl group as addition of an acylating agent to the NMR solution causes a downfield shift of these signals. Another AB complex centered at δ 3.14 shows the presence of an adjacent hydrogen atom and so must be the methylene group which is attached to sulfur but which becomes a methyl group on desulfurization. A third methylene group generates a doublet of doublets (δ 3.85 and 4.02) which must arise from a methylene having no adjacent hydrogen atoms so it must be attached to the two sulfur atoms. Oxidation of sparsomycin with hydrogen peroxide forms a product which was shown by analysis, ir spectrum, mass spectrum, and hydrolysis to **2b** to be the derivative of sparsomycin produced by oxidation of the two sulfur atoms to sulfones with no other change. This compound has a resonance in its NMR spectrum at δ 3.26 appropriate for CH_3SO_2,[6] but the signal present in sparsomycin's NMR spectrum at δ 2.30 is absent thus showing that the δ 2.30 resonance can be assigned to a CH_3S group. The presence of a $C_2H_5S_2O$ moiety containing CH_3SCH_2 suggests that in sparsomycin the group $CH_3SCH_2S{=}O$ is present, and this is confirmed by two facts. The acid hydrolysis of sparsomycin gives, among other products, formaldehyde, which would be expected as a product based on the work of Ogura and Tsuchihashi[7] if the above group were present. Furthermore, the chemical shift of δ 3.14 due to a methylene between H_2NCH and S would be more expected if the sulfur were present as sulfoxide.[6] The stereochemistry of the sulfoxide group was not established. The sum of these arguments leaves very little doubt that the structure of sparsomycin is as shown in the expression **1** although it is not intended that there be any suggestion as to the chirality of the sulfoxide group.

Irradiation of an aqueous solution of sparsomycin with an ordinary 15-W fluorescent desk lamp causes isomerization to isosparsomycin. Following the conversion by decrease in the ultraviolet peak at 302 nm led to the conclusion that about 60% of the material was present as isosparsomycin. Analysis indicated that the new product was an isomer as did its NMR spectrum which was almost identical with that of sparsomycin except for the signals due to olefinic hydrogen atoms. These signals in sparsomycin were a doublet of doublets centered at δ 7.24 and 7.45 with J = 16 Hz. In the isomeric compound the olefinic doublets have chemical shifts of δ 6.14 and 6.47 with J = 12 Hz. The decrease in the coupling constant shows that the conversion of sparsomycin to its isomer consists in isomerization of the trans olefin to a cis olefin.[8]

Experimental Section

Melting points are corrected.

Anhydrous Sparsomycin (1). A sample of sparsomycin prepared and dried as was done for the original analyses[2] contained 3.48% water. A sample of this composition was dried for 72 h at room temperature at 0.01 mm and analyzed.

Anal. Calcd for $C_{13}H_{19}N_3O_5S_2$: C, 43.21; H, 5.30; N, 11.63; S, 17.76; O, 22.14. Found: C, 43.32; H, 5.68; N, 11.41; S, 17.48; O, 22.11.

1,2,3,4-Tetrahydro-2,4-dioxo-6-methyl-5-pyrimidinecarboxylic Acid (2a) from Sparsomycin. A 1% aqueous solution of $KMnO_4$ was added dropwise to a suspension of 1 g of sparsomycin in 100 ml of water until a pink color persisted. About 250 ml of solution was required. A little ethanol was added to destroy excess $KMnO_4$, and the solution was filtered through diatomaceous earth. The filtrate was evaporated to dryness under reduced pressure, and the residue was dissolved in 100 ml of water. The resulting solution was stirred for about 2 h with 50 ml of Amberlite IR-120 (H^+). The supernatant was removed by decantation, and the resin was washed thoroughly with water. The combined supernatant and washings was filtered through diatomaceous earth, and the filtrate was concentrated under reduced pressure to a volume of about 5 ml. Refrigeration gave 236 mg. One charcoal treatment and two recrystallizations from water gave 119 mg: mp 242 °C dec; ir (Nujol) 3360, 3280, 3120, 1720, 1620, 1575, and 1515 cm^{-1}; uv (H_2O) max 267 nm (ϵ 8225), (0.1 N HCl) max 222 nm (ϵ 11 100), 272 (10 850), (0.1 N NaOH) max 288 nm (ϵ 6800); NMR (DMF-d_7) δ 2.70 (s, 3 H, CH_3), 12–13 (broad peak, 2–3 H, exchangeable); mass spectrum m/e 170 (M^+).

Anal. Calcd for $C_6H_6N_2O_4$: C, 42.36; H, 3.56; N, 16.47. Found: C, 42.49; H, 3.59; N, 16.47.

5-Hydroxymethyl-6-methyluracil (3). This was synthesized by a slight modification of Kircher's[9] procedure in which condensation of formaldehyde with 6-methyluracil was carried out in base. The sodium salt formed was dissolved in water and neutralized with the theoretical amount of acetic acid. The overall yield was 43%. It was found that Kircher's procedure was highly erratic and his yields could not be duplicated.

1,2,3,4-Tetrahydro-6-methyl-2,4-dioxo-5-pyrimidinecarboxaldehyde (4). A solution of 936 mg (6 mmol) of 5-hydroxymethyl-6-methyluracil in 80 ml of acetic acid was stirred while adding dropwise a solution of 400 mg (4 mmol) of CrO_3 in 40 ml of 50% acetic acid. The solution was then stirred at room temperature for 4 h followed by evaporation to dryness under reduced pressure at 35 °C. The residue was dissolved in 20 ml of water, and the solution was mixed thoroughly with 8 g of silica gel. The mixture was allowed to dry in a current of air with frequent stirring. The dried powder was added to a column containing 50 g of silica gel packed in a mixture of methyl ethyl ketone–acetone–water (7:2:1). The column was then eluted with the same solvent system collecting 103 5-ml fractions. Fractions 21–32 were combined on the basis of weight analysis and TLC on silica gel plates using the above solvents in the ratio 70:20:11. Evaporation of the pooled fractions under reduced pressure gave 378 mg of residue. Recrystallization from water gave 189 mg, mp >200 °C dec: R_f 0.60 (above system); ir (Nujol) 1740 cm^{-1} (CHO); uv (H_2O) max 231 nm (ϵ 6440), 283 (9500); NMR (DMF-d_7) δ 2.54 (s, 3 H, CH_3), 9.98 (s, 1 H, CHO); mass spectrum m/e 154 (M^+).

Anal. Calcd for $C_6H_6N_2O_3$: C, 46.76; H, 3.92; N, 18.18. Found: C, 47.16; H, 4.34; N, 17.87.

1,2,3,4-Tetrahydro-6-methyl-2,4-dioxo-5-pyrimidinecarboxylic Acid (2a). From 4. A mixture of 154 mg (1 mmol) of 4 and 10 ml of 0.1 N NaOH was stirred while slowly adding a solution of 106 mg (0.06 mmol) of $KMnO_4$ in 10.6 ml of water. A little ethanol was added to discharge the color, and the solution was filtered through diatomaceous earth. The filtrate was adjusted to pH 2.5 with 1 N HCl and evaporated to dryness under reduced pressure. The residue was triturated with 1.5 ml of water, and the mixture was filtered. The filter cake was washed with water and recrystallized from water after charcoal treatment: yield 28 mg (16%); mp 246 °C dec; ir and uv spectra identical with those of material isolated from sparsomycin; mass spectrum m/e 170.0286 (calcd for $C_6H_6N_2O_4$, 170.0323).

Anal. Calcd for $C_6H_6N_2O_4$: C, 42.36; H, 3.50; N, 16.47. Found: C, 42.50; H, 3.61; N, 16.32.

β-[(*E*)-1,2,3,4-Tetrahydro-6-methyl-2,4-dioxo-5-pyrimidine]acrylic Acid (2b). A. Acid Hydrolysis of Sparsomycin. A solution of 2 g of sparsomycin in 40 ml of 2 N HCl was heated on the steam bath for 2 h. The residue was diluted to 35 ml with water and allowed to stand for 3 days at room temperature. Filtration gave 370 mg (35%) of solid, mp 255–259 °C dec. Recrystallization twice from water, four times from DMF, and once from water gave 23 mg: mp 265 °C dec; R_f 0.32 (silica gel, EtOH–MeOH–H_2O, 50:45:5); pK_a' (DMF–60% EtOH), 7.90, 11.35; ir (Nujol) 3400, 3300, 3050, 1710, 1620, 1295, 1190, 1090, 1030, 985, 875, 830, and 780 cm^{-1}; uv (H_2O) max 293 nm (ϵ 14 210), sh 270 nm (ϵ 12 740); NMR (DMF-d_7) δ 2.40 (s, 3 H, CH_3C), 7.25 (d of d, 2 H, J = 16 Hz, trans HC=CH), 10.0–11.6 (broad, exchangeable H); mass spectrum m/e 152, 108, 81, 80, 44, 42.

Anal. Calcd. for $C_8H_8N_2O_4$: C, 48.98; H, 4.13; N, 14.28. Found: C, 48.68; H, 4.77; N, 14.11.

B. Basic Hydrolysis of Sparsomycin. A solution of 200 mg of sparsomycin in 20 ml of 1.0 N NaOH was heated under reflux for 8 h. The solution was adjusted to pH 3.0 with 1.0 N HCl and refrigerated for several days. The solid which separated was removed by filtration, wt 65 mg, mp 258–262 °C dec. The ir spectrum and the TLC R_f using the above system were identical with those of **2b** obtained by acid hydrolysis.

C. Synthesis. A mixture of 308 mg (2 mmol) of 4 and 1.39 g (4 mmol) of carbethoxymethylidenetriphenylphosphorane in 20 ml of dry Me_2SO was heated on the steam bath with protection from moisture for 6 h. Most of the Me_2SO was removed by evaporation under reduced pressure. The residue was diluted with 30 ml of water, and the solid precipitate was removed by filtration and recrystallized twice from EtOH: yield 68 mg (15%); mp 299–302 °C dec; R_f 0.41 (silica gel, Skellysolve B–acetone, 1:1); ir (Nujol) 3330, 1710, 1660, and 1620 cm^{-1}; uv (EtOH) max 303 nm (ϵ 17 875), sh 270 nm (ϵ 9400); NMR (Me_2SO-d_6) δ 1.20 (t, 3 H, CH_3CH_2), 2.28 (s, 3 H, CH_3C=), 4.13 (q, 2 H, CH_3CH_2), 7.13 (d of d, 2 H, trans HC=CH), 11.27 (s, 2 H, exchangeable), mass spectrum m/e 224 (M^+).

Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.50. Found: C, 53.93; H, 5.29; N, 13.08.

A solution of 300 mg of the above material (5) in 20 ml of 1 N NaOH was boiled for 2 h. The solution was acidified with excess concentrated HCl, allowed to stand for a few hours, and filtered, yield 240 mg. Recrystallization from water gave 151 mg (58%), mp 271 °C dec; the ir, uv, and NMR spectra of this product were essentially identical with those of the acid derived from hydrolysis of sparsomycin. The R_f values on silica gel TLC plates using methyl ethyl ketone–acetone–H_2O (70:20:11), EtOH–MeOH–H_2O (50:45:5), and MeOH–H_2O (9:1) were identical and were respectively 0.13, 0.40, and 0.75.

Anal. Calcd. for $C_8H_8N_2O_4$: C, 48.98; H, 4.13; N, 14.28. Found: C, 48.84; H, 4.52; N, 14.13.

Methyl β-[(*E*)-[1,2,3,4-Tetrahydro-6-methyl-2,4-dioxo-5-pyrimidine]acrylate. A mixture of 195 mg of **2b** and 20 ml of methanol was cooled in an ice bath while saturating with dry HCl. The mixture was allowed to stand at room temperature overnight. The solvent was removed by evaporation under reduced pressure, and the residue was repeatedly evaporated under reduced pressure with methanol. The product was recrystallized three times from methanol: yield 55 mg; mp 305–307 °C dec; ir (Nujol) 3330, 1720, 1660, and 1620 cm^{-1}; NMR (DMF-d_7) δ 2.40 (s, 3 H, CH_3C), 3.69 (s, 3 H, CH_3O), 7.28 (d of d, 2 H, J = 16 Hz, trans HC=CH), 11.15–11.34 (broad, 2 H, exchangeable); mass spectrum m/e 210.0676 (calcd for $C_9H_{10}N_2O_4$, 210.0644).

Anal. Calcd for $C_9H_{10}N_2O_4$: C, 51.42; H, 4.80; N, 13.20. Found: C, 51.22; H, 5.17; N, 13.35.

Di-*O*,*N*-Acetylcysteinol. One gram of sparsomycin was hydrolyzed as previously described for acid hydrolysis. After removal of **2b** the filtrate was evaporated to dryness under reduced pressure, and the residue was repeatedly evaporated under reduced pressure with methanol. The 554 mg of residue was mixed with 10 ml of dry pyridine and 2 ml of acetic anhydride, and the mixture was stirred overnight. Two milliliters of methanol was added, and the solution was evaporated to dryness under reduced pressure with frequent additions of methanol. The residue was mixed with 20 ml of water, and the mixture was extracted with four 20-ml portions of $CHCl_3$. The combined extracts were washed with two 10-ml portions of 0.1 N HCl and two 10-ml portions of water followed by drying ($MgSO_4$), filtration, and evaporation under reduced pressure. The residue (212 mg) was chromatographed on 10 g of silica gel using $CHCl_3$ until 100 5-ml fractions had been collected. The column was then developed with $CHCl_3$–MeOH (98:2) until a second 100 5-ml fractions had been collected. Fractions 28–50 of the second 100 were combined on the basis of a weight analysis and evaporated under reduced pressure, yield 110 mg. A portion of this was recrystallized from benzene: mp 99–100 °C; R_f 0.19 (silica gel, cyclohexane–EtOAc–95% EtOH, 5:3:2); ir (Nujol) 3230, 1740, 1645, and 1545 cm^{-1}; NMR ($CDCl_3$) δ 1.97 (s, 3 H, CH_3CO), 2.05 (s, 3 H, CH_3CO), 2.82–3.08 (m, 2 H, CH_2S), 4.15–4.65 (m, 3 H, OCH_2CHN), 6.73 (d, 1 H, NH).

Anal. Calcd for $C_7H_{13}NSO_3$: C, 43.98; H, 6.85; N, 7.32; S, 16.78. Found: C, 44.05; H, 6.70; N, 7.06; S, 16.54.

Formaldehyde from Sparsomycin. Two grams of sparsomycin was hydrolyzed with acid as already described. After **2b** had been

removed, the filtrate was extracted with 20 ml of benzene and three 20-ml portions of ether. One-fourth of the remaining aqueous phase was diluted with 300 ml of Brady's reagent. After the mixture had stood at room temperature for 3 days, it was filtered to give 103 mg of solid, mp 163–165 °C. Recrystallization from alcohol did not change the melting point. A mixture melting point with authentic formaldehyde 2,4-dinitrophenylhydrazone was not depressed, and the two compounds had identical ir spectra.

β-[(*R*)-*N*-(2-Hydroxy-1-methylethyl)-1,2,3,4-tetrahydro-6-methyl-2,4-dioxo-5-pyrimidine]propionic Acid (2d). A mixture of 400 mg of sparsomycin, 8 g of Raney nickel, and 200 ml of water was boiled and stirred for 21 h. The Raney nickel was removed by filtration and was washed with two 50-ml portions of boiling water. The combined filtrate and washings were evaporated to dryness under reduced pressure. The residue was dissolved in 50 ml of methanol, and the solution was filtered through diatomaceous earth. The filtrate was concentrated under reduced pressure, and the residue (188 mg) was recrystallized from methanol: yield 32 mg; mp 231 °C; mass spectrum *m/e* 255.1223 (calcd for $C_{11}H_{17}N_3O_4$, 255.1219).

Anal. Calcd for $C_{11}H_{17}N_3O_4$: C, 51.76; H, 6.71; N, 16.46. Found: C, 50.89; H, 5.47; N, 16.20.

Methane from Sparsomycin. A mixture of 16 g of Raney nickel and 400 ml of water was stirred and heated to boiling. Sparsomycin (760 mg, 2 mmol) was added. The gas which evolved was collected. There was obtained 105 ml (theoretical for 4 mmol 98.8 ml) of gas identified by its ir spectrum as methane containing a little carbon dioxide.

β-(1,2,3,4-Tetrahydro-6-methyl-2,4-dioxo-5-pyrimidine)-propionic Acid (2c). From 2d. Crude **2d** (600 mg) was dissolved in 40 ml of 1.0 N NaOH, and the solution was boiled for 8 h. After the reaction mixture had cooled, it was filtered. The filtrate was adjusted to pH 3.5 with concentrated HCl and concentrated under reduced pressure to 3–4 ml. Refrigeration gave 230 mg. Charcoal treatment and several recrystallizations from water gave 99 mg: mp 302–304 °C dec; ir (Nujol) 3050, 1720, 1630, 1530, 1375, 1340, 1280, 1210, 1175, 870, 815, 792, and 775 cm^{-1}; uv (H_2O) max 266 nm (ε 8237); NMR (Me_2SO-d_6) δ 2.08 (s, 3 H, CH_3C), 2.26–2.60 (m, 4 H, CH_2CH_2), 10.63 (s, 1 H, exchangeable), 10.91 (s, 1 H, exchangeable); mass spectrum *m/e* 198.0646 (calcd for $C_8H_{10}N_2O_4$, 198.0640).

Anal. Calcd for $C_8H_{10}N_2O_4$: C, 48.49; H, 5.09; N, 14.14. Found: C, 48.51; H, 5.17; N, 14.14.

Ethyl β-(2-Methylmercapto-6-methyl-4-oxo-5-pyrimidine)propionate. *S*-Methylisothiourea sulfate (21 g, 0.075 mol) was dissolved in 225 ml of water. Diethyl α-acetylglutarate (11.5 g, 0.15 mol) and 16.8 g (0.3 mol) of potassium hydroxide were added. The mixture was stirred overnight at room temperature and heated for 1 h on the steam bath. The mixture was refrigerated, and the supernatant was decanted. The residue was crystallized from EtOH, yield 1.7 g, mp 168 °C. Two recrystallizations from EtOH did not change the melting point: uv (EtOH) max 235 nm (ε 9216), 288 (8450); NMR (Me_2SO-d_6) δ 1.18 (t, 3 H, CH_3C), 2.22 (s, 3 H, CH_3C), 2.37–2.62 (m, 7 H, CH_3S and CH_2CH_2), 4.06 (q, 2 H, OCH_2CH_3), 11.66–12.81 (broad, 1 H, NH).

Anal. Calcd for $C_{11}H_{16}N_2SO_3$: C, 51.57; H, 6.30; N, 10.93; S, 12.54. Found: C, 51.72; H, 6.38; N, 11.11; S, 12.48.

1,2,3,4-Tetrahydro-6-methyl-2,4-dioxo-5-pyrimidinepropionic Acid (2c). Synthesis. A mixture of 2.5 g of ethyl β-(2-methylmercapto-6-methyl-4-oxo-5-pyrimidine)propionate and 50 ml of concentrated HCl was boiled for 8 h. Refrigeration gave 1.55 g, mp 295–297 °C dec. Recrystallization from water and DMF gave mp 303–305 °C dec; ir and NMR spectra were identical with those of **2c** from **2d**; mass spectrum *m/e* 198 (M^+).

Anal. Calcd for $C_8H_{10}N_2O_4$: C, 48.49; H, 5.09; N, 14.14. Found: C, 48.54; H, 5.24; N, 14.30.

Tribenzoyl-(*R*)-alaninol (8a). The filtrate from the hydrolysis of **2d** to give **2c** was freeze dried. A mixture of the residue with 20 ml of dry pyridine and 2 ml of benzoyl chloride was heated for 2 h on the steam bath. The pyridine was removed by evaporation under reduced pressure, and the residue was partitioned between 10 ml of $CHCl_3$ and 20 ml of water. The aqueous layer was extracted with two 10-ml portions of $CHCl_3$. The combined $CHCl_3$ layers were washed with 10 ml of 1 N HCl, 10 ml of saturated $NaHCO_3$ solution, and two 10-ml portions of water and dried ($MgSO_4$). After the solution was filtered and evaporated to dryness under reduced pressure, the residue (1.17 g) was chromatographed on 60 g of silica gel using $CHCl_3$ as the eluent. After 150 5-ml fractions were collected, fractions 65–82 were combined on the basis of a weight analysis and TLC (R_f 0.18, silica gel, $CHCl_3$). Evaporation of the pool under reduced pressure gave 282 mg which was recrystallized twice from EtOH: yield 86 mg; mp 87–89 °C; R_f 0.75 (silica gel, $CHCl_3$–MeOH, 95:5) identical with that of **8b**; $[\alpha]_D$ −61.4° (c 1, $CHCl_3$); ir (Nujol) 1720 (ester CO), 1660 (amide CO), 1595, and 1575 cm^{-1}; NMR ($CDCl_3$) δ 1.52 (d, 3 H, CH_3), 4.40–5.40 (m, 3 H, CH_2CH), 6.9–8.0 (m, 15 H, aromatic); mass spectrum *m/e* low resolution 387, 330, 265, 252, 208, 160, 105, 77, high resolution 387.1483 (calcd for $C_{24}H_{21}NO_4$, 387.1470).

Tribenzoyl-(*S*)-alaninol (8b). This was done essentially as was the preparation of **8a** but using 3 g of (*S*)-alaninol, 15 ml of benzoyl chloride, 150 ml of dry pyridine, and proportional amounts of other materials. Chromatography was done on 550 g of silica gel and 437 20-ml fractions were collected. Fractions 201–310 were combined and evaporated to dryness under reduced pressure, yield 9.6 g. Four recrystallizations from EtOH gave 2.6 g: mp 90–91 °C; TLC (see **8a** preparations); $[\alpha]_D$ +63.2° (*c* 2, $CHCl_3$); ir, NMR, and mass spectrum were the same as for tribenzoyl-(*R*)-2-aminopropanol (**8a**); mass spectrum *m/e* 387.1495 (calcd for $C_{24}H_{21}NO_4$, 387.1470).

Anal. Calcd for $C_{24}H_{21}NO_4$: C, 74.40; H, 5.46; N, 3.62. Found: C, 74.35; H, 5.83; N, 3.93.

Periodate Oxidation of 2d Hydrolysate. After removal of **2c** from the hydrolysate of **2d** derived from 200 mg of sparsomycin, sodium periodate (0.43 g, 2 mmol) was added, and the solution was allowed to stand overnight. Nitrogen was bubbled through the reaction mixture and then through 200 ml of Brady's reagent for 4 h. Filtration gave 14 mg of yellow solid, mp 148–150 °C. A mixture melting point with authentic acetaldehyde 2,4-dinitrophenylhydrazone (mp 152–154 °C) was 148–150 °C while a mixture melting point with the propionaldehyde derivative (mp 149–151 °C) was 131–136 °C.

The aqueous residue after removal of acetaldehyde was adjusted to pH 10 with NaOH solution. The solution was steam distilled into 10 ml of 0.1 N HCl until no more volatile base was distilled. Filtration indicated that 0.3 mmol of volatile base had been distilled. The solution was again made strongly basic with NaOH solution and steam distilled into a solution of 140 mg of *p*-hydroxyazobenzene-*p'*-sulfonic acid in 25 ml of water. The solution was evaporated to dryness under reduced pressure, and the residue was recrystallized twice from water. The ir spectrum of the product was identical with that of ammonium *p*-hydroxyazobenzene-*p'*-sulfonate.

Peroxide Oxidation of Sparsomycin. One gram of sparsomycin was dissolved in 90 ml of acetic acid and 10 ml of 30% H_2O_2 was added. After the solution had stood at room temperature for 1 day, it was evaporated to dryness at room temperature under high vacuum. The residue was triturated with water and again evaporated to dryness under reduced pressure. This procedure was repeated twice. One recrystallization from water gave 680 mg of which 180 mg was again recrystallized from water to give 102 mg: mp 251 °C dec; $[\alpha]_D$ +45° (c 0.5, H_2O); ir (Nujol) 3500, 3210, 1720, 1660, 1585, 1300, 1225, 1155, 1135, 1055, 1022, 975, 865, and 783 cm^{-1}; uv (H_2O) max 301 nm (ε 22 600) sh 270 (14 050); NMR (Me_2SO-d_6) δ 2.24 (s, 3 H, CH_3C), 3.25 (s, 3 H, CH_3SO_2); mass spectrum *m/e* 409 (calcd, 409).

Anal. Calcd for $C_{13}H_{19}N_3S_2O_8$: C, 38.12; H, 4.68; N, 10.26; S, 15.66; O, 31.26. Found (corrected for 3.18% water content): C, 38.40; H, 4.96; N, 10.13; S, 15.58; O, 33.08.

An acid hydrolysis of 500 mg of the peroxide product using the same procedure as was used to convert sparsomycin to **2b** gave 90 mg of material which had the same R_f in TLC in EtOH–MeOH–H_2O (50:45:5) as **2b**. Recrystallization from water with charcoaling gave 32 mg of product which had the same NMR spectrum as **2b** and the same R_f values in TLC as **2b** in the system already mentioned.

Isosparsomycin. A solution of 500 mg of sparsomycin in 750 ml of water was irradiated with a fluorescent desk lamp for 7 days. The solution was evaporated to dryness under reduced pressure. The residue was subjected to countercurrent distribution in a 10 ml per phase machine using the system ethyl acetate–butanol–water (3:7:10) for 400 transfers. Tubes 46–80 (K = 0.19) were pooled and evaporated to dryness under reduced pressure giving 247 mg of amorphous residue. The residue was dissolved in 5 ml of hot water, and the solution was filtered through diatomaceous earth. Slow evaporation of the filtrate at room temperature gave a crystalline precipitate. Recrystallization from water gave 91 mg: mp 158–164 °C; R_f 0.16 (silica gel; *n*-BuOH–EtOH–H_2O, 70:27:3); ir (Nujol) 3375, 3325 (sh), 1745, 1710, 1675, 1640, 1555, 1525 (sh), 1445, 1425, 1370, 1310, 1270, 1245, 1098, 1065, 1018, 1002, 975, 955, 895, 750, and 725 cm^{-1}; NMR (DMF-d_7) δ 2.11 (s, 3 H, CH_3C), 2.30 (s, 3, CH_3S), 3.10 (m, 2 H, $CHCH_2SO$), 3.65 (m, 2 H, CH_2O), 3.95 (d of d, 2 H, $SOCH_2S$), 4.35 (m, 1 H, CHNH), 6.31 (d of d, 2 H, J = 12 Hz, cis HC=CH).

Anal. Calcd for $C_{13}H_{19}N_3O_6S_2$: C, 41.37; H, 5.08; N, 11.14; S, 16.99. Found: C, 42.09; H, 5.32; N, 11.13; S, 17.28.

Registry No.—1, 1404-64-4; 1 peroxide derivative, 58462-94-5; **2a**, 51622-67-4; **2b**, 28277-67-0; **2b** Me ester, 28425-66-3; **2c**, 28181-39-7; **2d**, 28277-69-2; **3**, 147-61-5; **4**, 24048-74-6; **5**, 28277-68-1; **6** *O,N*-di-

acetyl derivative, 58462-95-6; **8a**, 29537-31-3; **8b**, 28277-70-5; ethyl β-(2-mercapto-6-methyl-4-oxo-5-pyrimidine)propionate, 58462-96-7; *S*-methylisothiourea sulfate, 867-44-7; diethyl α-acetylglutarate, 1501-06-0; benzoyl chloride, 98-88-4; (*S*)-alaninol, 2749-11-3; isosparsomycin, 58462-97-8.

References and Notes

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Sigmatropic Hydrogen Migration and Electrocyclization Processes in Compounds in the Vitamin A Series. Photochemistry of Polyenes. 10[1]

V. Ramamurthy and R. S. H. Liu*[2]

Department of Chemistry, University of Hawaii, Honolulu, Hawaii 96822

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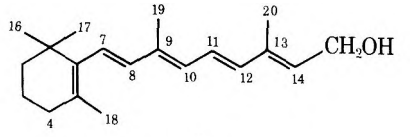
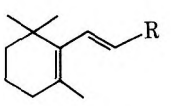
Reactions of dienes, trienes, and tetraenes in the vitamin A series brought about by direct irradiation were examined. In addition to the previously known sigmatropic 1,5-hydrogen migration from C-18 to C-8 and the hitherto unnoticed electrocyclization, geometric isomerization also appears to be an important reaction from S_1. Electrocyclization and geometric isomerization are reversible processes; hence in most cases the end products are retro-γ derivatives. Mechanistically it was shown that the hydrogen migration process can originate from either the 7-cis or 7-trans isomers of the conjugated systems. A case of 6e-electrocyclic ring opening process involving both the excited states of the product and the reactant is presented.

Compounds in the vitamin A (I) series are known to undergo a variety of photochemical reactions. In addition to the geometric isomerization reactions, which appear to be the exclusive reaction of the triplet states,[3] direct irradiation leads to hydrogen migration, cyclization, and intramolecular cycloaddition products. In this paper, the sigmatropic 1,5-hydrogen migration and 6e-electrocyclization processes are examined.

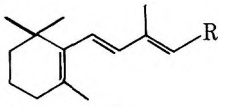


I



II

a, R = $COCH_3$
b, R = $CHCH_3OH$
c, R = CN

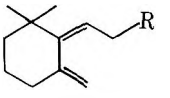


III

a, R = CN
b, R = CO_2Et
c, R = CO_2H
d, R = H
e, R = CHO
f, R = $COCH_3$

The earliest report on hydrogen migration in compounds in this series was on β-ionone (IIa) in 1957,[4] but its correct structure, a retro-γ derivative (IVa), was not recognized until 4 years later.[5] In this case, it is a minor product, the major being the α-pyran V which was later shown to be in equilibrium with *cis*-ionone.[6] In a series of papers in the early 1960's, Mousseron-Canet and co-workers[7] established the generality of the sigmatropic hydrogen migration reaction in trienes (β-ionylidene derivatives, III) as well as dienes in the vitamin A series. Furthermore, because of detection of 7-cis isomer(s) prior to significant accumulation of the retro-γ products, they suggested that the retro-γ products are formed by way of the 7-cis isomer(s) in two separate photochemical steps.

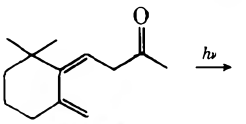
The initially formed retro-γ products are believed to have the *Z* configuration. This was deduced from their lack of re-



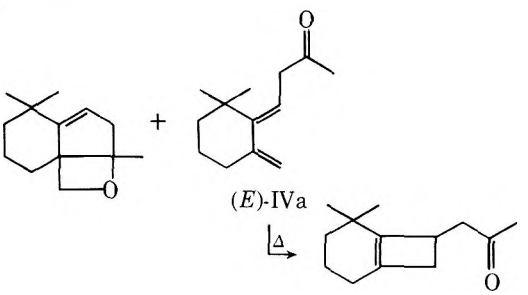
(*Z*)-IV

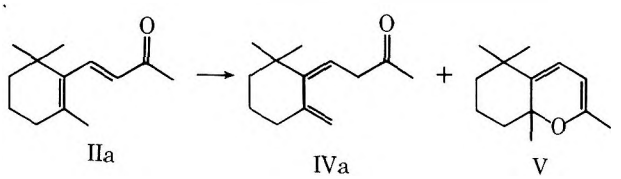
a, R = $COCH_3$
b, R = $CHCH_3OH$
c, R = CN

activity toward maleic anhydride.[7a] More recently, it was found that (*Z*)-retro-γ-ionone undergoes secondary photochemical reactions of geometric isomerization and internal cycloaddition giving (*E*)-retro-γ-ionone and the tricyclic ether shown.[8] Upon heating, (*E*)-retro-γ-ionone [(*E*)-IVa] further rearranged to a cyclobutene[8]—one of few cases where a cyclobutene is more stable than the corresponding diene.[9]



IVa, *Z*





IIa IVa V

Table I. Characteristic NMR Data of (*Z*)-Retro-γ-ionyl (IV) and -ionylidene (V) Derivatives[a]

Registry no.	Compd	H-7	CH_2-8,8	H-10	Exo CH_2	CH_3-19
		γ-Ionyl				
	IVa[b]	5.33 (t)	3.16 (d)		4.96, 4.51	
35986-44-8	R = $COCH_3$	$J_{7,8}$ = 7.1 Hz				
	IVb	5.18 (t)	2.18 (d)		4.53, 4.91	
35986-46-0	R = $CHCH_3OH$	$J_{7,8}$ = 7.0				
	IVc	5.72 (t)	3.13 (d)		5.15, 5.58	
58503-66-5	R = CN	$J_{7,8}$ = 7.0				
		5.23 (t)	3.10 (d)		4.45, 4.85	
58503-67-6	R = CO_2H	$J_{7,8}$ = 7.0				
		5.20 (t)	3.28 (d)		4.50, 4.82	
58503-68-7	R = C_6H_5	$J_{7,8}$ = 7.0				
		5.18 (t)	2.20 (d)		4.40, 4.75	
58503-69-8	R = $(CH_3)_2COH$	$J_{7,8}$ = 6.5				
		γ-Ionylidene				
58503-70-1	R = CN, 9-trans	5.12 (t)	3.93 (d)	5.04	4.50, 5.00	1.96
58503-71-2	9-cis	5.12 (t)	3.20 (d)	5.04	4.56, 4.92	1.80
		$J_{7,8}$ = 7.5				
58503-72-3	R = CO_2Et, 9-trans	6.16 (t)	3.01 (d)	5.68	4.62, 5.00	2.19
58503-73-4	9-cis	6.23 (t)	3.60 (d)	5.68	4.26, 5.00	1.86
		$J_{7,8}$ = 7.5				
58503-74-5	R = CO_2H, 9-trans	5.19 (t)	3.08 (d)	5.72	4.62, 5.02	2.22
58503-75-6	9-cis	5.26 (t)	3.64 (d)	5.72	4.62, 5.08	1.92
		$J_{7,8}$ = 7.0				
58503-76-7	R = H	5.24 (t)	2.82 (d)	4.68	4.60, 4.94	1.70
		$J_{7,8}$ = 7.5				

[a] HA-100. In $CDCl_3$–Me_4Si. δ in parts per million, in *J* in hertz. [b] Data of P. de Mayo, J. B. Stothers, and R. W. Yip, *Can. J. Chem.*, **39**, 2135 (1961).

During the course of our investigation we found photochemical 6e-electrocyclization also to be an important reaction in compounds in the series. (The formation of the α-pyran from *cis*-ionone is probably a thermal process.) In selected systems other secondary internal cycloaddition reactions were also observed and have been reported elsewhere.[10]

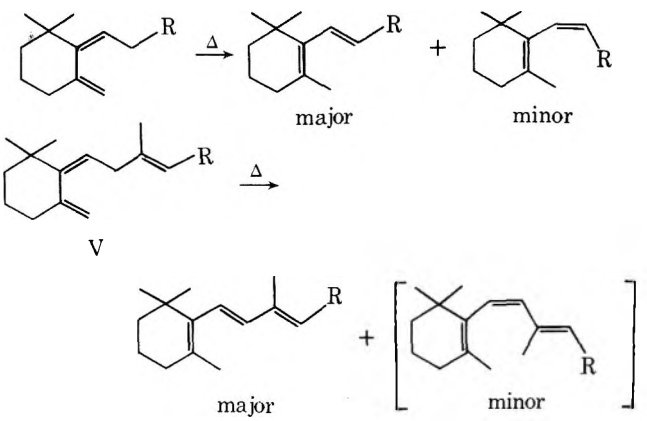
Results

β-Ionol (IIb) and Other Dienes. Direct irradiation (254 nm) of an ether solution of the cis isomer was found to give the same retro-γ-ionol as from trans-ionol. GLC was used to follow the reaction. The trans isomer was not found to be present during any stage of irradiation.

The uv absorption spectrum of *trans*-β-cyclocitrylideneacetonitrile (IIc) is sufficiently different from those of *cis*-IIc and the retro-γ product so that the use of Pyrex filters allows selective excitation of the trans. Under such conditions the product mixture was found to contain 35% *cis*-IIc[11] and 65% of IVc (NMR data listed in Table I). This ratio is independent of the solvent used ($CDCl_3$, CD_3OD, CD_3CN, C_6D_6, and *n*-butyl bromide). Upon removal of the Pyrex filter (in CD_3OH and CD_3CN) IVc became the only product. Similarly irradiation of *cis*-IIc in a quartz vessel gave initially *trans*-IIc as well as IVc; but the final product was again only the retro-γ product.

Our results on *trans*-β-ionone (IIa) are in agreement with those in the previous reports.[4-6] However, additionally we also found that starting from an equilibrium mixture of *cis*-ionone and the α-pyran, retro-γ-ionone (IVa) can also be obtained. The reaction was initially accompanied by formation of *trans*-IIa.

β-Ionylideneacetonitrile (IIIa) and Other Trienes. Direct irradiation of the trienes IIIa–d was examined. The end products were the corresponding retro-γ products. We confirmed the observation of efficient geometric isomerization of IIIb giving all four isomers during early stages of irradiation. Similar behavior exists in the other three compounds. However, sometimes the reaction is further complicated by the presence of another primary photoproduct. Since this product probably involves a hitherto unnoticed reaction in compounds in this series and the process appears to be most efficient in β-ionylideneacetonitrile (IIIa), we examined the latter system in some detail. The ^1H NMR data of isomers of β-ionylideneacetonitrile are in the literature.[11] The assignment of its retro-γ products (V) was based on analogy of its NMR spectrum (Table I) with those of other known retro-γ products (those from β-ionone, ethyl β-ionylideneacetate, and β-ionylideneethanol).[7c] For example, the original doublets of H-7 and H-8 are now replaced by three vinyl hydrogens, two in the high-field region (4.5–5.0 ppm) characteristic of terminal methylenes and the remaining one a triplet. The latter is coupled with a new methylene doublet around 3 ppm and the methyl-18 signal is no longer present. The geometry around C-7 is believed to be trans for the same lack of reactivity toward a dienophile as noted earlier[7a] and also for its behavior in thermal rearrangement. Upon heating an inert solution of the compound to ~130 °C a mixture of the geometric isomers of IIIa was formed. This reverse hydrogen migration is, in fact, characteristic of all retro-γ derivatives of compounds in this series (see below).



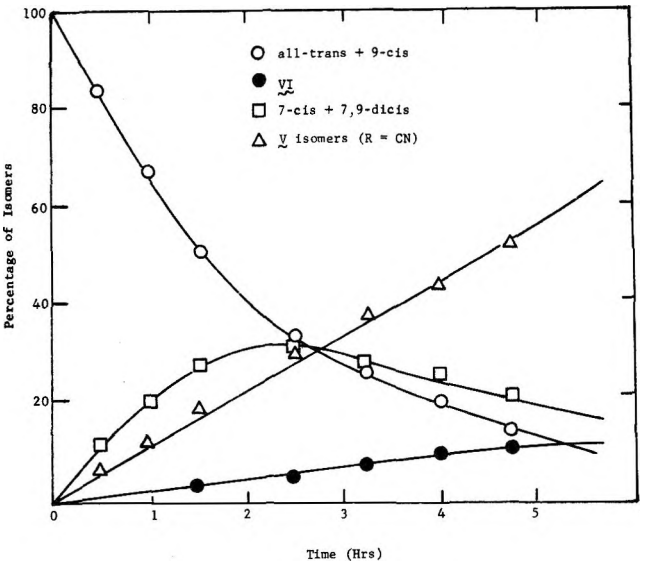


Figure 1. An action plot of direct irradiation of a mixture of the two 7-trans isomers of β-ionylideneacetonitrile (IIIa).

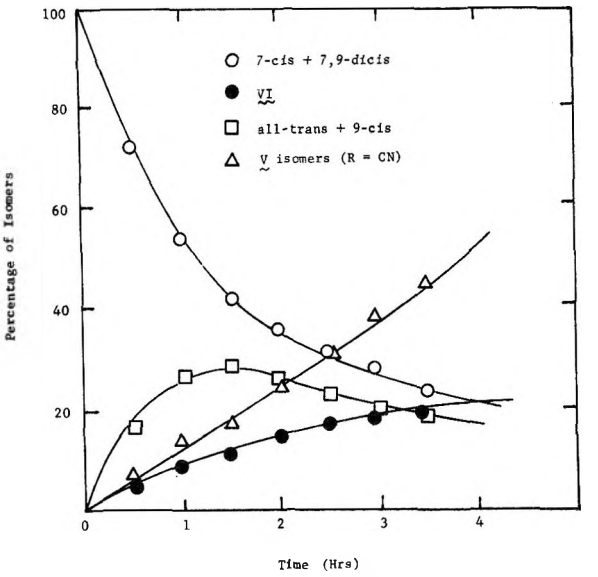


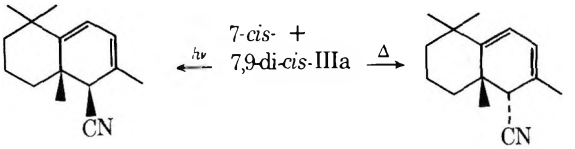
Figure 2. An action plot of direct irradiation of a mixture of the two 7-cis isomers of β-ionylideneacetonitrile (IIIa).

Since the *E* isomer of a retro-γ product is expected to undergo ring closure to a cyclobutene, we conclude that the initial photoproducts must also have the *Z* configuration.

Careful examination of the NMR of the *E*-retro-γ product revealed the presence of two isomers. The CH_3-19 signal appears as two unequal singlets. This is not surprising in view of the fact that two isomers (all trans and 9-cis) are present in the starting trienes. They are therefore geometric isomers around the same double bond. Configurational assignments were based on the chemical shift of CH_3-19. It shifts downfield when the group is cis to the substituent at C-10. An explanation based on change of electron density around the hydrogens in CH_3-19 (steric polarization) has been advanced to account for the change in chemical shift.[12] The key NMR data of the retro-γ products from IIIa and also other triene derivatives are listed in Table I along with those of dienes.

The course of reaction of IIIa was followed by NMR. Geometric isomerization was the major process at early stages of irradiation giving substantial amounts of the two 7-cis isomers. Then, formation of the retro-γ product was accompanied by a new product, VI. The latter apparently was photolabile. Its buildup reached a maximum amount of ~20% and then diminished with other triene nitriles. At the end only the retro-γ products remained. The slope of the lines in an action plot of this reaction (Figure 1), however, suggests that all three types of products are primary photoproducts. Similar results were obtained when starting with a mixture of the two 7-cis isomers (Figure 2).

Attempts to isolate the new product presented some difficulties. By repeated column chromatography, a fraction containing about equal amounts of VI and a mixture of the retro-γ isomers was obtained. After comparison of the NMR spectra of the mixture and the retro-γ isomers the following information about VI was obtained. The compound contains four different methyl groups, therefore the geminal dimethyl groups are no longer equivalent. The shift of CH_3-18 signal to δ 1.1 indicates that it is now attached to a saturated carbon. The CH_3-19 signal remains at 1.92. Two vinyl hydrogens are present, appearing as a singlet. The H-10 signal is now a singlet in the saturated region (3.22 ppm). These features are only in agreement with a cyclized cyclohexadiene structure. We have also observed that thermal rearrangement of a mixture of 7-*cis*- and 7,9-di-*cis*-β-ionylideneacetonitrile resulted in the formation of a single product. Its ^1H NMR spectrum closely resembles that of VI. Again, four different methyl groups are present with CH_3-18 now shifted to a higher field and CH_3-19 appearing ~0.1 ppm upfield from the corresponding signal in VI. The two vinyl hydrogens are nonequivalent but close in chemical shift and the coupling constant is that normally found for 2,3 hydrogens in cyclohexadienes. This thermal product coming from a different electronic state is probably an epimer of VI.[13] For reasons delineated in the Discussion section, the photoproduct (VI) is believed to have the stereochemistry shown and the thermal product, its epimer VIa.

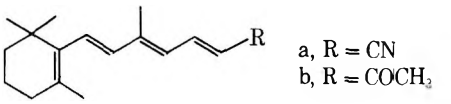


VI VIa

By direct irradiation of the thermal product, VIa, the cyclohexadiene products were shown to undergo reverse ring opening reactions.[14] The course of the reaction was followed by NMR. The results were shown in the action plot.[14]

Trienal IIIe and trienone IIIf were found not to undergo electrocyclization nor sigmatropic rearrangements under direct irradiation. Geometric isomerization appears to be the only important characterizable photochemical reaction.

β-Ionylidenecrotononitrile (VIIa) and Other Tetraenes. The tetraenenitrile under direct irradiation again



VII

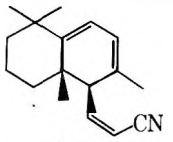
resulted in efficient geometric isomerization and 6e-electrocyclization. The irreversible hydrogen migration in this case is relatively an inefficient process; therefore the product mixture passes through a stage containing substantial amounts of the cyclized product(s). They are partially isolable by column chromatography. In one attempt two useful fractions were collected. One contained essentially a single isomer, the NMR data of which are listed in Table II. The features informative of the structure are (1) the presence of four nonequivalent methyls, (2) the presence of a low-field methine doublet (δ 3.28) which was shown by decoupling experiments to be coupled with a vinyl hydrogen, (3) the same vinyl hydrogen is coupled to another vinyl hydrogen with J = 11 Hz,

Table II. Characteristic NMR Data of the Electrocyclized Products[a]

Registry no.	Compd	H_7	H_8	H_{10}	H_{11}	H_{12}	CH_3-19	CH_3-18	CH_3-16,17
43161-05-3	VI[b]	5.78	5.78	2.56			1.92	1.10	
43161-06-4	VIa	5.72	5.80	2.51			1.82	1.11	1.00
		$J_{7,8}$ = 5.5 Hz							1.04
58503-77-8	VIII	5.72	5.80	3.28	6.70	5.42	1.66	1.16	0.98
		$J_{7,8}$ = 5.5		$J_{10,11}$ = 11.0		$J_{11,12}$ = 11.2			1.14
58526-11-7	VIIIa[c]	5.72	5.80	3.32	6.74	5.32	1.68	1.18	0.98
		$J_{7,8}$ = 5.5		$J_{10,11}$ = 11		$J_{11,12}$ = 17			1.14

[a] HA-100. In $CDCl_3$–Me_4Si. [b] From a mixture of VI and retro-γ-ionylideneacetonitrile. [c] From a mixture of VIII and VIIIa.

indicative of the cis geometry. These features are in agreement with the structure VIII shown. In analogy with the photo-



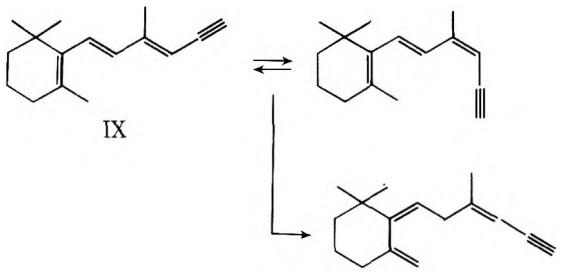
VIII

product from IIIa, the stereochemistry about the new bond is believed to be cis.

The second fraction contained a mixture of two compounds, VIII being one of them. From the difference of the spectra of the two fractions we gathered the spectral data for the second photoproduct, also listed in Table II. With the exception of the coupling constants between H-11 and H-12, it closely resembles that of VIII. It is probably a geometric isomer of VIII. The larger vinyl coupling constant ($J_{11,12}$ = 17 Hz) suggests that it is the trans isomer (VIIIa).

Prolonged irradiation again led to retro-γ products as indicated by the characteristic NMR features as discussed for the trienes. However, the mixtures were too complex and not separable for complete configurational assignments.

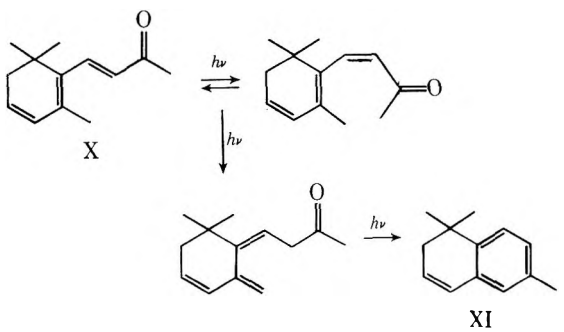
Irradiation (254 nm) of the all-trans isomer of the hydrocarbon IX led to isomerization around the 9,10 bond with a slower rate of formation of only the retro-γ products. The two



IX

isomers of the latter could not be separated, but the NMR spectrum of the mixture was sufficiently informative [H-7 (t) 5.2; CH_2-8,8′ (d) 3.2, 2.9; CH_3-19 1.74, 1.90; exo-CH_2 4.6, 5.2, and 4.98]. Irradiation (>300 nm) of the C_{18}-tetraene ketone, VIIb, on the other hand, only caused photoisomerization around the 9,10 and 11,12 double bonds.

3,4-Dehydro-β-ionone (X). Its photochemistry was discussed in some detail in an earlier preliminary paper.[15] The



XI

initial geometric isomerization and hydrogen migration are followed by a secondary photoreaction giving the hydrocarbon XI. With properly filtered light (Pyrex) the reaction could be made to terminate at the retro-γ-dehydroionone stage.

Discussion

The Retro-γ Products. In agreement with earlier studies by Mousseron-Canet and co-workers[7] we found sigmatropic hydrogen migration from methyl-18 to C-8 to be a general reaction in compounds in the vitamin A series. The only exceptions are the aldehydes and ketones where the only identifiable reaction is geometric isomerization. Based on the results described above some generalizations can be made.

Although quantum yields have not been determined, the relative efficiencies of the reaction appear to be of the order of dienes, trienes, and then tetraenes. In no instances did we observe formation of retro-γ products from pentaenes in the series. Neither were there reports on such reactions in longer carotenoids.[7a] This trend of reactivity parallel with the energy content of the excited singlets is not a surprising one especially in view of the considerable activation involved in similar ground state reactions. However, other factors probably also affect the efficiency of the reaction. For example, of the two trienones, β-ionylideneacetone (IIIf) and dehydro-β-ionone (X), only the latter undergoes hydrogen migration. The small difference in ring chain conformation expected for the two systems may have an effect on the reactivities of the two compounds, but we suspect that a more important factor is the difference in electron density at C-8 in the excited states of the two molecules. In dehydro-β-ionone C-8 is a terminal carbon of the triene unit (or the third atom in the trienone) while in IIIf the same carbon is in the middle of the triene unit (same for the trienone); therefore the electron density at C-8 in X should be higher. Electron density probably also partly accounts for the high reactivity of β-ionyl derivatives and the higher reactivity of β-ionol than β-ionone.

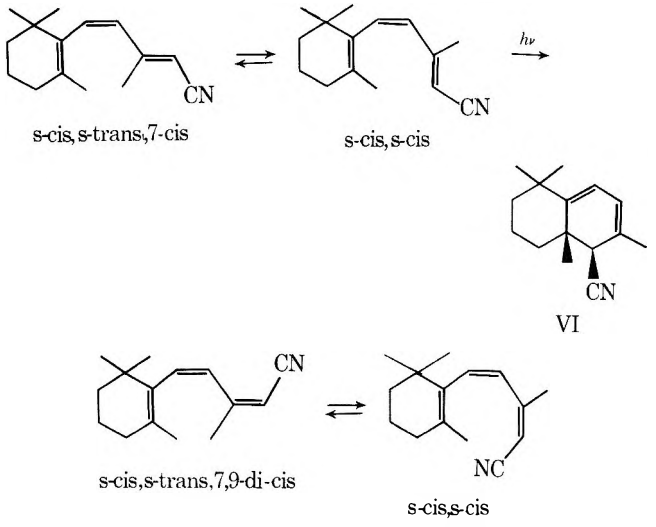
We have no evidence to support the postulate that retro-γ products are only derived from the 7-cis isomers.[7] The observation of the 7-cis isomers prior to significant accumulation of the retro-γ products clearly is not a sufficient condition for the postulate. In fact, that the 7-cis isomers were not detected in other systems would force one to conclude that geometric isomerization was the rate-determining step in this postulated mechanism of two consecutive steps of photoreaction. This is quite contrary to known reactivity of polyenes, the quantum yield of geometric isomerization being generally higher than other concerted processes.[18] Symmetry rules do not impose any restriction to hydrogen migration from either isomer. Furthermore molecular models do not suggest reasons to suspect that the antarafacial process[13] should be more favored from the 7-cis isomer. Our results with β-citrylideneacetonitrile (IIc) in which the 7-trans isomer was selectively excited clearly showed that the retro-γ product can directly come from the 7-trans isomer. Furthermore, the observation of formation of retro-β-ionol from 7-*cis*-β-ionol without detectable amounts of 7-*trans*-β-ionol strongly suggests that retro product can also

originate directly from the 7-cis isomer. We therefore believe that hydrogen migration can proceed from either isomer. It generally represents a leakage from the reversible geometric isomerization process. However, in some instances, where molecules are especially suitable for hydrogen migration (e.g., β-ionol with high energy content and high electron density at C-8) this leakage becomes the predominant process.

The thermal rearrangement of the retro-γ product back to the corresponding β-ionol and β-ionylidene derivatives should now involve suprafacial 1,5-hydrogen migration.[13] Same as the photochemical reaction, it shows little selectivity resulting in the formation of both the 7-cis and the 7-trans isomers. The 7-cis isomers of trienes understandably further rearranged immediately after formation to cyclohexadienes (see below).

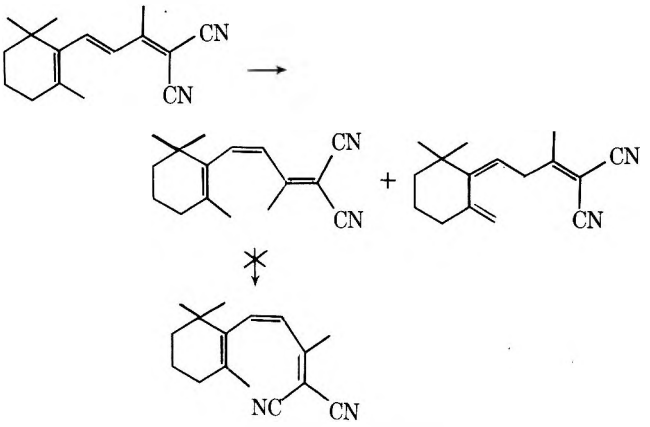
Electrocyclization Products. The reversible photochemical 6e-electrocyclization process is of course a well-known reaction in trienes and higher polyenes. In fact, examples of these were important in the formulation of the Woodward–Hoffmann rule on electrocyclization.[13] However, the case we described in β-ionylideneacetonitrile apparently represents the first example of such a reaction in compounds in the vitamin A series.

The action plots of photoreactions of the 7-trans and the 7-cis isomers of the trienenitrile are shown in Figures 1 and 2, respectively. The more rapid rise of the curve of the electrocyclized products in Figure 2 than the corresponding curve in Figure 1 appears to suggest that the photoelectrocyclization occurs only from the 7-cis isomers. Therefore, starting from the 7-trans isomers two separate photochemical steps are required.[17] Furthermore, that only one geometric isomer of the cyclized product is formed suggests that only one of the two 7-cis isomers is reactive. Consideration of probable ground state conformation of the two isomers and the necessary conformation for electrocyclization provides the answer. The

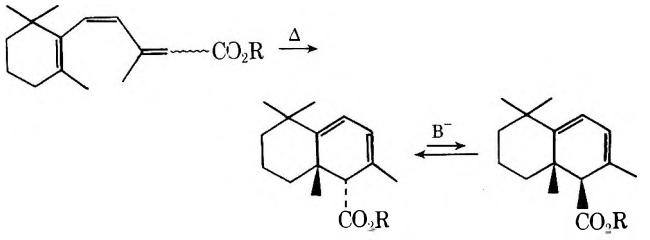


7-cis isomer may exist in conformations resembling either the s-cis,s-trans or the s-cis,s-cis conformer while the 7,9-di-cis isomer is likely to exist only in the less crowded s-cis-s-trans conformation. However, only the di-s-cis conformer can be excited to the now conformationally rigid di-cis singlets necessary for cyclization.[18] Therefore, only 7-cis cyclizes giving according to the rule the conrotatory product VI. For the same reason, thermal cyclization is expected to proceed only from 7-cis giving the disrotatory product VIa. However, that the thermal reaction did proceed to completion suggests that geometric isomerization from 7,9-di-cis to 7-cis takes place concurrently with electrocyclization at elevated temperatures.

In agreement with the above explanations, we found that β-ionylidenemalononitrile where the s-cis,s-cis conformer of even the 7-cis isomer is not likely to exist does not undergo photochemical electrocyclization. In this case, the only primary photochemical processes are geometric isomerization and sigmatropic hydrogen migration. Also, in agreement with



the above interpretation is the recent work of Frater where the same 6e-electrocyclization was observed in a related system of a mixture of 7-*cis*- and 7,9-di-*cis*-β-ionylideneacetate.[16] The thermal product, assigned with the same stereochemistry as VIa, was epimerized in the presence of a base to give a small amount of a product which spectroscopically is in agreement with the compound with the opposite stereochemistry thus equivalent to VI.

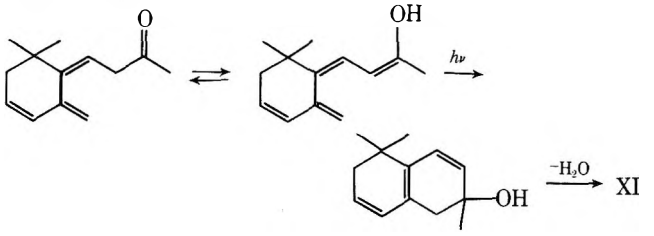


Figures 1 and 2 also show that the cyclization process is photochemically reversible. After prolonged irradiation, products from the less efficient but irreversible sigmatropic process predominate. This process is more clearly demonstrated by irradiation of the thermal product VIa. Triene products were followed by the appearance of the retro products.[14] The rule for 6e-electrocyclization predicts the formation of the 7,9-di-cis isomer of IIIa from conrotatory ring opening of VIa. However, it was shown earlier[14] that all four geometric isomers appear almost concurrently. This apparent violation of the rule was explained by assuming that the ring-opened product is formed in its excited singlet state which is capable of further reactions. From a cyclohexadiene to a hexatriene, energetically this is a downhill process thus not suffering from the same difficulty as in excited state conversion of butadiene to cyclobutene, pointed out by Dauben.[19]

Our study and also previous studies show that the photochemistry of dienes and trienes in this series is marked by the absence of other types of products commonly observed in the photochemistry of dienes and triene (e.g., cyclobutene, bicyclobutane, and bicyclo[3.1.0]hexane products). We believe that this is due to the ground state conformation of the unsaturated C_5–C_{10} unit in these compounds. From space filling molecular models and also shown by NMR studies,[20] it is believed that the 5,6 and 7,8 double bonds are far from coplanar (whether the cisoid or the transoid form) for concerted reactions to cyclobutenes or bicyclobutanes. On the other hand, there is little difficulty for electronic overlap between C_5 and C_{10} in a 7-cis isomer in a Möbius manner[21] giving the cyclohexadiene with the cis stereochemistry. Models also show that any conformation involving close proximity of C_5 and C_9 (i.e.,

the s-cis-s-trans conformation necessary for formation of bicyclo[3.1.0]hexenes)[22] only results in even closer proximity of C_9 and hydrogens on C_{18}. We believe that this accounts for the formation of the sigmatropic hydrogen migration products and not the internal cycloaddition products.

Lastly, the formation of dehydro-γ-ionone (XI) from dehydroretro-γ-ionone is clearly a photoprocess (the retro product is thermally stable). It probably involves photoelectrocyclization of the enol followed by dehydration catalyzed by trace acids.



Experimental Section

Procedures to prepare the compounds used in this study are in the literature.[11,23] Low-pressure Hg lamps (PCQ-X1, uv-Products Inc.) were used for 254-nm irradiation and medium-pressure Hg lamps (Hanovia) for >300-nm irradiation. For longer wavelengths appropriate Corning filter plates were used to isolate light of the desired wavelengths. For dienes, GLC was used to follow the course of reaction; and for longer polyenes, NMR was used instead. Column conditions and chemical shifts have been described previously.[3,11] The following are representative procedures of direct irradiation at preparative scale.

Retro-γ-ionol (IVb). A 2% ether solution of 7-*cis*-β-ionol was irradiated with 254-nm light in a manner similar to that described for the trans isomer.[7b] The reaction was followed by GLC (6 ft, 3% SE-30, 128 °C) and is usually completed within 2 days of irradiation. The product was isolated by short-path distillation. Its properties are identical with those described in the literature for IVb.[7b]

Retro-γ-ionylideneacetonitrile (V, R = CN) was prepared by irradiation (254 nm) of an ether solution of a mixture of 7-trans (or 7-cis) isomers of β-ionylideneacetonitrile in a similar manner as described above. The NMR data of the products are listed in Table I. When the same triene was irradiated with light >300 nm (Pyrex filters), the final product mixture contained the retro-γ product (77%) and another new compound (23%). Since these compounds cannot be separated by, e.g., column chromatography on silica gel, the characteristic NMR signals of the latter (Table II) were obtained after comparison of the spectrum of the mixture with that of V. Based on these spectral data and other related information (see text) the cyclohexadiene structure VI was assigned to the new product. Upon removal of the Pyrex filters the final product mixture was found to contain only V (R = CN).

β-Ionylideneacetaldehyde (IIIe). A deoxygenated 5% solution of a mixture of *all-trans*- and 9-*cis*-β-ionylideneacetaldehyde in perdeuterated benzene in a NMR sample tube was irradiated with >300-nm light. Formation of the two 7-cis isomers was detected immediately by their characteristic methyl signals. No other new products were detected (by NMR) even after 2 days of irradiation when the solution darkened considerably.

Tetraenenitrile VIIa. The tetraenenitrile, obtained as a four-isomer mixture from Horner reaction of *all-trans*- and 9-*cis*-β-ionylideneacetaldehyde with diethylcyanomethyl phosphonate, was irradiated with >300-nm light and the reaction was followed by NMR. The absence of methyl signals around 1.5 ppm indicated that the 7-cis isomers were not present in significant amounts at any stage of irradiation.[11] Signals in other region were too complex to provide any useful information. After 1 day of irradiation the mixture was separated by column chromatography on silica gel (Biosil) using hexane–benzene (3:1) solvent mixture. The small amounts of unreacted tetraenes were thus separated. Of the products, two useful fractions were collected. One fraction was found to contain primarily one compound. Its spectral properties were discussed in the text and are only consistent with the cyclized structure VIII [ir 2215 (CN), 760 cm^{-1} (cis disubstituted double bond); NMR (Table II)]. The second fraction contained about equal amounts of VIII and a second product which is believed to be the 11-trans isomer of VIII (see text).

Acknowledgments. The work was partially supported by the Public Health Service (Grants EY00918, AM17806). V.R. was a recipient of a departmental fellowship from funds made available from the NSF-DSD Grant (NSF GU 3855) awarded to the Chemistry Department, University of Hawaii.

Registry No.—IIa, 79-77-6; IIb, 472-80-0; IIb 7-cis isomer, 35031-11-9; IIc, 40244-29-9; 7-*trans*,9-*trans*-IIIa, 5299-98-9; 7-*trans*,9-*cis*-IIIa, 5299-99-0; 7-*cis*,9-*trans*-IIIa, 40244-68-6; 7-*cis*,-9-cis-IIIa, 40244-51-7; IIIa, 58526-71-9.

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Proton Inventory Study of a Water-Catalyzed Hydrolysis

F. M. Menger*[1] and K. S. Venkatasubban

Department of Chemistry, Emory University, Atlanta, Georgia 30322

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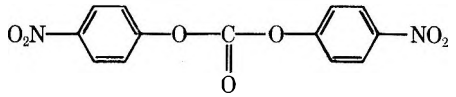
The neutral water reaction of bis(4-nitrophenyl) carbonate in H_2O–D_2O has been subjected to a proton inventory analysis. A plot of observed rate constants vs. the atom fraction of deuterium is linear, indicating that a single proton contributes to the solvent isotope effect of 2.24. This result is not consistent with a "one-water" mechanism nor with a "two-water" cyclic concerted mechanism but does agree with a "two-water" general base mechanism in which the transition state is reached at an early stage. It was also shown that urea, tetraalkylammonium salts, KBr, and other structure-making or structure-breaking additives cause only minor changes in the hydrolysis rates. These data suggest that hydrolytic enzymes do not achieve appreciable rate accelerations by perturbing the water structure at their active sites.

"Water reactions" refer to hydrolyses in which only substrate and water participate.[2,3] Acidic and basic catalysis play no role. Labile carboxylic acid derivatives such as acetic anhydride,[4] acetylimidazole,[5] ethyl trifluoroacetate,[6] and δ-thiovalerolacetone[7] all react with water at 25 °C. The hydrolyses are characterized by sizable negative entropies of activation and by solvent isotope effects greater than unity (typically, $\Delta S^{\ddagger} = -30$ to -45 eu and $k_{H_2O}/k_{D_2O} = 2$–3).[2] One virtue of water reactions is their relatively simple mechanism.[8] Another is their potential usefulness in the study of water properties.[9] In the present paper we describe a "proton inventory" of the hydrolysis of bis(4-nitrophenyl) carbonate (I)



I

at a pH where the neutral water reaction dominates. Proton inventories require the measurement of reaction rates in several different mixtures of protium oxide (water) and deuterium oxide. This information discloses the number of protons contributing to the solvent isotope effect.[10,11] We also determined the rates of the water reaction of I in the presence of large amounts of urea, tetramethylammonium chloride, and other structure-making or structure-breaking additives.

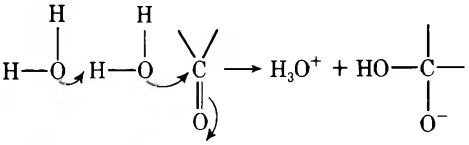
Experimental Section

Materials. Bis(4-nitrophenyl) carbonate (I) was prepared by the method of Fife and McMahon.[12] The carbonate, crystallized twice from benzene, melted at 139–141 °C (lit.[12] mp 138–140 °C). Alkaline hydrolysis of the material produced 2 molar equiv of *p*-nitrophenoxide. Acetonitrile (Eastman Spectrograde) was purified by distillation over P_2O_5 and K_2CO_3. Deuterium oxide (99.7%) and deuterium chloride (99%) were purchased from Diaprep. All inorganic salts were dried in an oven and organic additives (except the tetramethylammonium salts) were crystallized or distilled prior to use.

Kinetics. Hydrolysis rates of I were measured by following the appearance of *p*-nitrophenol at 320 nm using a Cary 14 spectrophotometer fitted with a 1.0 slidewire. A 3.00-ml solution of 0.01 N HCl in an appropriate mixture of D_2O–H_2O was equilibrated in a 1.00-cm cuvette placed within the thermostated cell chamber of the Cary 14. Reactions were initiated by adding 20 μl of a concentrated solution of I in acetonitrile with the aid of a small glass stirring rod. Concentrations of I in the cuvette were approximately 3×10^{-5} M. We followed the reactions to greater than 80% completion, and took infinity values at 10 half-lives. First-order rate constants, calculated in the usual manner, were reproducible to within 3% in most cases. Mr. Josef Nemeth, Urbana, Ill., determined the atom fraction of deuterium in a "pure" DCl/D_2O solution.

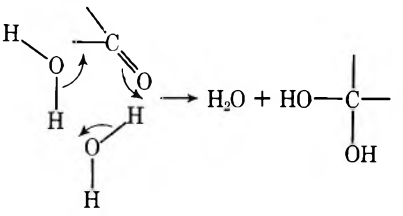
Results and Discussion

Water reactions of labile carboxylic acid derivatives, including I, are believed to involve *two* water molecules as shown in eq 1.[12] One water molecules functions as a general base



(1)

whereas the other functions as a nucleophile. This mechanism accords with a solvent isotope effect greater than unity and with the known susceptibility of labile substrates to general base catalysis. Yet neither line of evidence precludes kinetic equivalents of eq 1 such as the cyclic concerted process in eq 2.[13,14] In fact, even a "one-water" mechanism is consistent with



(2)

a solvent isotope effect near 2 provided that the bond between the water oxygen and the carbonyl carbon is well formed in the transition state. These ambiguities prompted us to carry out a "proton inventory" experiment in order to secure the total number of protons contributing to the solvent isotope effect.

A proton inventory is a rather specialized physical organic method, and a brief discussion of its attributes might be useful.[10,11,15] The observed rate constant k_n in a H_2O–D_2O mixture is related to the rate constant k_0 in pure water by eq 3.

$$k_n/k_0 = \prod_i^{TS} (1 - n + n\phi_i^*) \Big/ \prod_j^{GS} (1 - n + n\phi_j) \qquad (3)$$

The parameter n signifies the atom fraction of deuterium. All transition state protons i that contribute to the isotope effect possess a term in the right-hand numerator of eq 3. These terms are multiplied as are the terms in the denominator corresponding to the reactive ground state protons j. Each proton site is associated with an isotopic fraction factor ϕ which expresses the degree of deuteration of the site. For example, since ϕ for $R_2OH^+ = 0.69$, the $[R_2OD^+]/[R_2OH^+]$ ratio equals 0.69 (not 1.0) in a 50% D_2O/50% H_2O mixture. Lists of fractionation factors for various types of exchangeable protons can be found elsewhere.[11] Analysis of the water reaction of bis(4-nitrophenyl) carbonate is particularly simple because the substrate has no reactive protons and the other reactant, water, has a $\phi = 1$ by definition. Consequently, the denominator is unity and we need consider only the protons of the transition state. If only one proton in the transition state contributes to the solvent isotope effect, then a plot of k_n vs. n should be linear. Nonlinearity would arise from two or more transition state terms in eq 3.

Table I. Observed First-Order Rate Constants for the Hydrolysis of Bis(4-nitrophenyl) Carbonate in Mixtures of 0.01 N HCl/H_2O and 0.01 N DCl/D_2O at 50.0 °C[a]

Atom fraction of deuterium (n)	No. of runs	$k_n \times 10^4$, min^{-1}
0.000	10	1795 ± 47[c]
0.099	3	1696 ± 32
0.198	4	1604 ± 20
0.297	3	1501 ± 14
0.395	3	1382 ± 20
0.494	4	1278 ± 32
0/593	4	1172 ± 30
0.692	3	1066 ± 20
0.791	3	987 ± 21
0.889	2	874 ± 10
0.986[b]	20	802 ± 20

[a] Ionic strength = 0.05 with KCl. [b] Atom fraction of deuterium in "100%" 0.01 N DCl/D_2O was determined by J. Nemeth, Urbana, Ill. Other n values are based on this number. [c] Error limits are standard deviations.

Most of our kinetic studies of I were carried out in 0.01 M aqueous HCl at 50.0 °C. We are certain that the hydrolysis is a true neutral water reaction under these conditions because the observed rates in 0.10 N HCl, 0.01 N HCl, 0.001 N HCl, and at pH 4.65 and 5.29 differ only slightly (0.177, 0.180, 0.178, 0.185, and 0.186 min^{-1} at 50.0 °C, respectively). The latter two rate constants were secured using an acetate buffer and extrapolating to zero buffer concentration (acetate catalyzes the hydrolysis by a general base mechanism[12]). Fife and McMahon[12] obtained a k_{obsd} = 0.168 at 0.01 N HCl and 50.0 °C, a satisfactory agreement. The solvent isotope effect, k_{H_2O}/k_{D_2O}, was found to equal 2.24 which is substantially smaller than the value of 2.88 published previously.[12] The source of the discrepancy remains unclear.

Table I lists first-order rate constants, k_n, for the water reaction of I at different atom fractions of deuterium. Since a plot of k_n vs. n (Figure 1) is linear,[16,17] we conclude that only a *single* proton contributes to the solvent isotope effect. Let us now consider the significance of this result with respect to possible transition states of the water reaction. In the general base mechanism (eq 1) the solvent isotope effect must derive solely from the proton which is transferred from the "nucleophilic" water to the "general base" water. The fact that

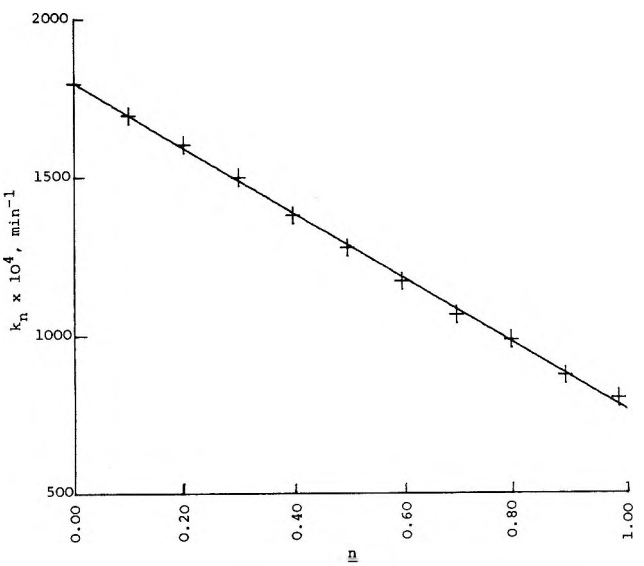


Figure 1. Dependence of k_n on the atom fraction of deuterium n in mixtures of protium and deuterium oxides. The data are taken from Table I.

Table II. Effect of Additives on the Water-Catalyzed Hydrolysis of Bis(4-nitrophenyl) Carbonate in 0.01 N HCl at 50.0 °C

Registry no.	Additive	Concn, M	$k_{obsd} \times 10^4$, min^{-1}
	None		1794 ± 47[a]
7758-02-3	KBr	0.99	1393 ± 21
	KBr	2.00	922 ± 54
7447-40-7	KCl	0.99	1642 ± 31
75-05-8	CH_3CN	1.00	1511 ± 23
67-68-5	DMSO	1.12	1891 ± 58
123-91-1	Dioxane	1.03	1312 ± 51
75-65-0	t-BuOH	1.04	1487 ± 60
57-13-6	Urea	1.00	1950 ± 43
	Urea	3.00	2008 ± 13
	Urea	4.00	2176 ± 91
	Urea[b]	4.00	1195
632-22-4	Tetramethylurea	1.03	1934 ± 13
75-57-0	Tetramethylammonium chloride	1.00	1730 ± 30
	Tetramethylammonium chloride	2.00	1550 ± 60
1643-19-2	Tetrabutylammonium bromide	1.00	1110 ± 34

[a] Error limits are standard deviations from usually three runs. [b] Hydrolysis carried out in D_2O; single run only.

our inventory detected no secondary isotope effect from the three remaining water protons signifies that extensive proton transfer to the "general base" water is not achieved in the transition state. Otherwise both protons of the "general base" water would be transformed into hydronium-like protons. Their fractionation factor would then change from 1.0 in the ground state to a value resembling 0.69 in the transition state, and a three-proton inventory would have been observed. Note that the fourth proton in eq 1 (namely the nontransferred proton on the "nucleophilic" water) is converted from an –OH proton of water into an –OH proton of a tetrahedral intermediate; one would not expect the site to add an important term to eq 3. In summary, the linear k_n vs. n plot is indeed consistent with a general base mechanism provided that the transition state is reached at an early stage of the reaction.[18] Moreover, we can eliminate a "one water" hydrolysis with considerable bond formation between the oxygen and the carbonyl carbon because this would lead to a two-proton inventory. Lack of a two-proton inventory also renders unlikely a cyclic concerted mechanism (eq 2) in which two protons are transferred.

We carried out a set of peripheral experiments to determine if additives that perturb water structure also perturb the water reaction rates of I. The data are presented in Table II. Tetraalkylammonium ions, strong structure-making species,[19] are seen to decrease the hydrolysis rates. Urea, an effective structure-breaker,[20] increases the rates. Dioxane and KBr do not fit this pattern; they are weakly structure-breaking[21] and yet decrease the rates. The most striking feature of Table II is the small variation in rate constants. Several explanations for this are possible. (1) The water reaction of I does not require properly oriented water molecules. Hence the hydrolysis is insensitive to the diffusional average water structure. (2) The water reaction does in fact demand two properly oriented water molecules, but these molecules are members of solvation shells encasing the substrate. If the structure of the solvation shell is only slightly affected by the additives, their presence will not change k_{obsd}. (3) The additives modify $\Delta H^{\ddagger}$ and $T\Delta S^{\ddagger}$ in a compensatory manner so that the rate effects are small. Engbersen and Engberts[9] have shown clearly that this

third factor is important. However, from the point of view of catalysis, which is concerned primarily with rates and not the component activation parameters, the lesson from Table II and the work of others[22,23] is clear. Nonreactive additives have a disappointing rate effect on the water reactions of carboxylic acid derivatives.[24] Our data suggest that hydrolytic enzymes do not achieve appreciable rate accelerations by perturbing the microscopic environment at the active sites.[25]

Acknowledgment. This work was supported by a grant from the National Science Foundation (GP-42919X) and from the National Institutes of Health (GM-20336 and GM-21457).

Registry No.—I, 5070-13-3; water, 7732-18-5.

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(16) Analysis of the data in Table I by means of a polynomial regression program indicates that quadratic and higher terms in eq 3 are insignificant. We thank Professor R. L. Schowen and Mr. Daniel P. Quinn for carrying out these calculations.
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Metalation of Cumene with *n*-Pentylsodium in the Presence of *N,N,N′,N′*-Tetramethylethylenediamine. Preparation of α-Cumylsodium

Timothy F. Crimmins*[1] and Coretta M. Chan

Chemistry Department, University of Wisconsin, Oshkosh, Wisconsin 54901

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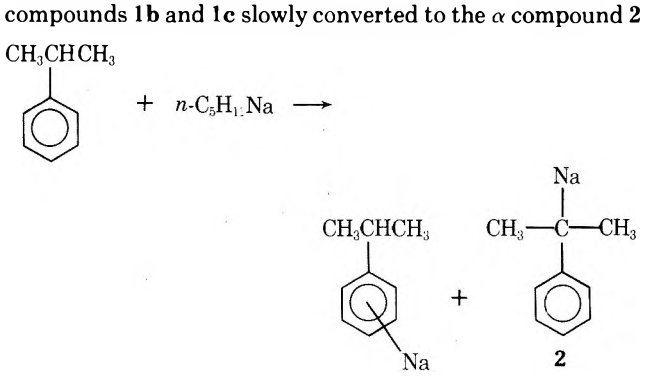
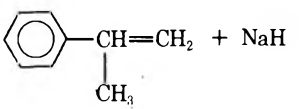
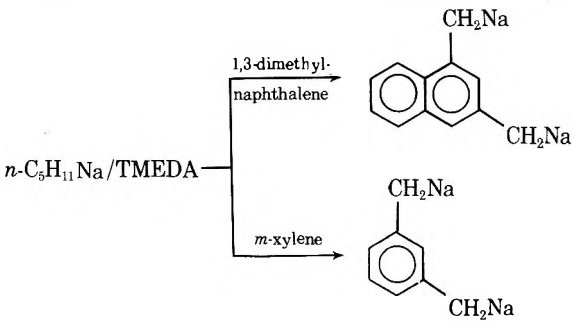
The metalation of cumene with *n*-pentylsodium was reinvestigated to assess the effect of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) on this reaction. It was found that in the presence of TMEDA, cumene was metalated by *n*-pentylsodium giving a 65% yield of α-cumylsodium with an isomeric purity of 95% after a 24-h reaction period. In the initial stages of the reaction, a kinetically controlled metalation occurred giving principally *o*-, *m*-, and *p*-isopropylphenylsodium. At longer reaction times, these compounds isomerized to α-cumylsodium in a thermodynamically controlled process.

In 1963 Professor Benkeser and co-workers[2] reported that cumene was metalated by *n*-pentylsodium in a kinetically controlled process to give a mixture of *m*- and *p*-isopropylphenylsodium (**1b** and **1c**) and trace amounts of α-cumylsodium (**2**). In the presence of excess cumene, the ring sodium compounds **1b** and **1c** slowly converted to the α compound **2** in a thermodynamically controlled process. The α-sodium compound was shown to be unstable and decomposed to α-methylstyrene and sodium hydride.[3]





Recently, Trimitsis and co-workers[4] reported that the presence of *N,N,N′N′*-tetramethylethylenediamine (TMEDA) greatly altered the reactivity of *n*-pentylsodium in metalation reactions. Thus, 1,3-dimethylnaphthalene and

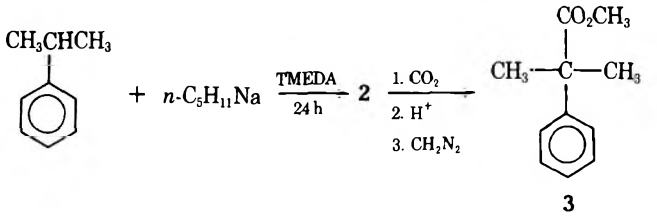


m-xylene were quantitatively dimetalated by *n*-pentylsodium in the presence of TMEDA. In the absence of TMEDA, monometalation occurred in low yield. This observation is in general agreement with several other laboratories who reported that TMEDA greatly activated organolithium reagents in metalation reactions.[5]

In view of the rather dramatic effect which TMEDA had on the metalation of 1,3-dimethylnaphthalene and *m*-xylene, we were prompted to reinvestigate the metalation of cumene by *n*-pentylsodium in the presence of TMEDA. The general objectives of this research were to assess the effect of TMEDA on the stability of α-cumylsodium and the kinetic vs. thermodynamic factors operating in the presence of this reagent.

Results and Discussion

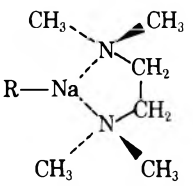
When cumene was metalated with *n*-pentylsodium in the presence of TMEDA for 24 h, *α-cumylsodium (2) was produced in a 65% yield and with an isomeric purity of 95%* as adjudged by the formation of methyl 2-methyl-2-phenylpropanoate (3) upon carbonation and esterification of the



3

reaction. The identity of **3** was proven by comparing its VPC retention time and NMR and ir spectra with those of an authentic sample of this compound. Small quantities of *m*-isopropylphenylsodium (**1b**, 3%) and *p*-isopropylphenylsodium (**1c**, 2%) were also formed based on VPC analysis of the methyl esters obtained upon carbonation and esterification. Practically all of the *n*-pentylsodium was consumed in the metalation reaction as adjudged by the relatively small quantity of methyl hexanoate observed in the gas chromatogram.[6] In addition, VPC analysis revealed that only trace amounts of α-methylstyrene were produced during the course of the reaction indicating that the α-cumylsodium was not decomposing to any significant degree. When this reaction was run in the absence of TMEDA, only a 40% yield of metalation products was obtained consisting of 55% of the meta compound **1b**, 45% of the para compound **1c**, and none of the α compound **2**. Additionally, a large quantity of *n*-pentylsodium remained unreacted.

The stability of the α-cumylsodium and the increased reactivity of the *n*-pentylsodium observed under our reaction conditions apparently result from complex formation between TMEDA and the organosodium compounds. In the case of



R = *n*-pentyl or α-cumyl

α-cumylsodium one could speculate that this complex is responsible for increasing the ionic character of the benzylic carbon–sodium bond, thus permitting benzylic resonance to play a more significant role in stabilizing the α-cumyl carbanion. In a similar manner, complex formation between TMEDA and *n*-pentylsodium may increase the ionic character and thus the basicity of the *n*-pentylsodium. This would be reflected in a more reactive metalating reagent and hence higher yields of product. Alternately, it could be argued that the TMEDA breaks down the highly associated *n*-pentylsodium into smaller, more reactive aggregates. These arguments parallel those used by Trimitsis[4] and Benkeser[7] in explaining their observations in the organosodium reactions which they studied.

Table I. Metalation of Cumene by *n*-Pentylsodium in the Presence of TMEDA as a Function of Time[a]

Time, h	1a, %	1b, %	1c, %	2, %
1	3 (3)[b]	57 (57)	33 (34)	7 (6)
2	3	42	26	29
4	0	11	9	80
6	0 (0)	2 (5)	2 (5)	96 (90)
12	0 (0)	2 (2)	1 (2)	97 (96)
18	(0)	(1.5)	(0.5)	(98)
24	0 (0)	2 (1)	1 (1)	97 (98)

[a] The values reported in this table were obtained by removing aliquots from the reaction at the stated times. Aliquots were not removed from the first experiment at 18 h and from the second experiment at 2 and 4 h. [b] Numbers in parentheses represent the results of a second experiment.

The metalation of cumene by *n*-pentylsodium in the presence of TMEDA was also studied as a function of time by removing aliquots from the reaction. Table I shows that after a 1-h reaction period, metalation occurred principally on the ring giving the ortho, meta, and para sodium compounds **1a**, **1b**, and **1c**.[8] In addition analysis of the 1-h aliquot showed that practically all of the *n*-pentylsodium was consumed based on the small quantity of methyl hexanoate observed in the gas chromatogram. At longer reaction times, the α-sodium compound **2** predominated. Since practically all of the *n*-pentylsodium was consumed in the early stages of this reaction metalation must have occurred initially on the aromatic ring of cumene in a kinetically controlled process. In the presence of TMEDA, the ring compounds **1a**, **1b**, and **1c** rapidly reverted to the more thermodynamically stable α-cumylsodium (**2**) presumably via a transmetalation sequence involving excess cumene.

These results are in sharp contrast to those of Broaddus,[9] who did not observe the ring to side chain isomerization in the metalation of a series of alkylbenzenes including cumene with *n*-butyllithium in the presence of TMEDA. The lack of isomerization in these reactions is most likely due to the lower reactivity of organolithium reagents compared to the corresponding sodium compounds. It is also of interest to note that the kinetically controlled product distribution which was observed in our metalation reaction after 1 h was very close to the kinetically controlled product distribution observed by Broaddus.

In summary, we have found that *cumene is metalated by n-pentylsodium in the presence of TMEDA to give α-cumylsodium in high yield and isomeric purity.* This metalation occurred initially in a kinetically controlled process on the aromatic ring of cumene followed by an isomerization of the sodium to the benzylic position of cumene in a thermodynamically controlled process.

Experimental Section

Organosodium reactions were run under a positive nitrogen pressure in a Morton flask fitted with a Stir-O-Vac (La Pine Scientific Co.) high-speed stirring apparatus. All glassware employed in these reactions was dried in an oven at 110 °C and flushed with nitrogen before use. Octane, 1-chloropentane, and cumene were purified by standard techniques and shown to be VPC pure. TMEDA was distilled from BaO or CaH_2 immediately before use.[10] NMR spectra were obtained on a Hitachi Perkin-Elmer R20-A spectrometer and ir spectra on a Perkin-Elmer 457 spectrometer.

Reference Compounds. Methyl *p*-isopropylbenzoate and methyl 2-methyl-2-phenylpropanoate were obtained by esterifying *p*-iso-

propylbenzoic acid (Eastman Kodak Co.) and α,α-dimethyl-α-phenylacetic acid (K and K Laboratories, Inc.) with diazomethane.[11] Methyl *o*- and *m*-isopropylbenzoate were prepared by treating *o*- and *m*-bromocumene with magnesium followed by carbonation and esterification with diazomethane. The o- and *m*-bromocumene compounds were prepared by adaptations of standard literature methods.[12]

Analytical Method. Metalation reactions were analyzed by carbonating the reaction mixtures and esterifying the resulting carboxylic acids with diazomethane.[13] The resulting methyl esters were analyzed on a F and M Model 720 gas chromatograph equipped with a 6-ft 15% diisodecyl phthalate column at 170 °C with a helium flow rate of 60 ml/min. The validity of this technique was demonstrated by the analysis of an authentic sample as follows:

Ester	Synthetic mixture, %	VPC analysis, %
α	31	31
o-	9	8
m-	30	31
p-	30	30

The yield of cumene methyl esters was obtained employing quantitative VPC analysis using ethyl benzoate as an internal standard. Analysis of a synthetic mixture of the four isomeric cumene methyl esters showed this technique to be reliable to within 5%.

***n*-Pentylsodium.** To a vigorously stirred 9.2-g (0.40 mol) sodium dispersion[14] in 125 ml of octane maintained at −10 to −20 °C was added 16 g (0.15 mol) of 1-chloropentane in 25 ml of octane over 1.5 h. After the addition of the 1-chloropentane, the mixture was stirred for an additional 0.5 h at −10 to −20 °C to ensure complete reaction.

Metalation of Cumene with *n*-Pentylsodium in the Presence of TMEDA. To a *n*-pentylsodium sample in 150 ml of octane was added 36 g (0.30 mol) of cumene and 13.9 g (0.12 mol) of TMEDA. The mixture was vigorously stirred for 24 h before being poured onto a dry ice–ether slurry. After the mixture warmed to room temperature, hydrolysis was effected[15] followed by separation of the organic and aqueous layers. The organic layer was washed three times with water and these washings were added to the aqueous layer. The combined aqueous layer was extracted three times with ether and these extracts combined with the original organic layer. The combined organic layer containing the neutral compounds was dried over Drierite before solvent was removed on a rotary evaporator. Analysis of the residue on a silicone gum rubber column at 100 °C revealed that only a trace of α-methylstyrene was produced. The combined aqueous layer was acidified with concentrated HCl and the resulting mixture was extracted five times with ether. The combined ether extracts which contained the acidic compounds were esterified with diazomethane and dried over Drierite, and solvent was removed on a rotary evaporator. VPC analysis of the resulting methyl esters showed that a 65% yield[16] of cumene methyl esters was obtained consisting of 95% methyl 2-methyl-2-phenylpropanoate (**3**), 3% methyl *m*-isopropyl benzoate (**1b**), and 2% methyl *p*-isopropylbenzoate (**1c**). Additionally, VPC analysis showed that only a small quantity of methyl hexanoate was present. Distillation of the methyl esters gave a sample of methyl 2-methyl-2-phenylpropanoate boiling at 92–94 °C (8 mm) which had an ir and NMR spectra superimposable with the ir and NMR spectra of an authentic sample of this compound.

Metalation of Cumene with *n*-Pentylsodium in the Absence of TMEDA. Cumene was metalated by *n*-pentylsodium in the absence of TMEDA using the above procedure. VPC analysis of the methyl esters showed that a 40% yield of cumene methyl esters was obtained consisting of 55% methyl *m*-isopropylbenzoate (**1b**) and 45% methyl *p*-isopropylbenzoate (**1c**). VPC analysis also revealed that large quantities of methyl hexanoate were present.

Metalation of Cumene with *n*-Pentylsodium in the Presence of TMEDA as a Function of Time. To a *n*-pentylsodium sample in 150 ml of octane was added 36 g (0.30 mol) of cumene and 13.9 g (0.12 mol) of TMEDA. Aliquots (20 ml) were removed and carbonated at various time intervals (see Table I) and after 24 h the reaction was carbonated. Workup, esterification, and analysis of the samples were performed in the usual manner. The results appear in Table I. Additionally, only trace amounts of methyl hexanoate were observed in the gas chromatogram in the 1-h aliquot.

Registry No.—**2**, 15544-84-0; TMEDA, 110-18-9; cumene, 98-82-8; *n*-pentylsodium, 1822-71-5.

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(10) In our hands it was observed that the activating effect of the TMEDA was greatly diminished if the TMEDA was not distilled from BaO or CaH_2 prior to use.
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(12) H. Gilman and A. H. Blatt, "Organic Syntheses", Collect. Vol. I, Wiley, New York, N.Y., 1941, pp 111, 133, and 135.
(13) Previous research has demonstrated that this carbonation and esterification technique is an accurate method to "tag" the location of the sodium in these highly reactive and air-sensitive organosodium compounds. See ref 2, 7, and 8b.
(14) M. Schlosser in "Newer Methods of Preparative Organic Chemistry", Vol. 5, W. Foerst, Ed., Verlag Chemie, Weinheim/Bergstr., Germany, and Academic Press, New York, N.Y., 1968, p 299.
(15) Prior to hydrolysis, a piece of dry ice was added to the breaker to produce a carbon dioxide atmosphere. This prevented fires resulting from the reaction of excess sodium with water.
(16) *n*-Pentylsodium was the limiting reagent in these reactions. Percentage yields of cumene esters were based on an assumed 70% (0.1 mol) yield of *n*-pentylsodium.

A Synthesis of Progesterone from Dehydroepiandrosterone

Michael L. Raggio and David S. Watt*

Department of Chemistry, University of Colorado, Boulder, Colorado 80309

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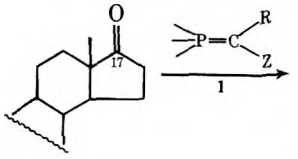
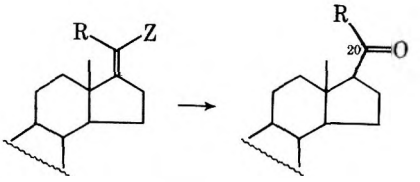
A direct two-carbon homologation of 17-keto androstanes to 20-keto pregnanes using the Wittig reaction would require a phosphorous reagent 1 bearing a masked carbonyl group Z as well as a methyl group (R = CH_3).[1] Alternative approaches



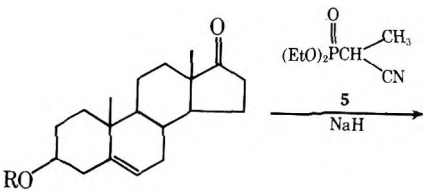


to this problem have utilized Wittig reagents bearing only a methyl group[2] (R = CH_3, Z = H) or only a masked carbonyl group[3] (R = H, Z = OCH_3). Further elaboration of the products of these Wittig reactions to 20-keto pregnanes has excluded the presence of a double bond elsewhere in the steroid[2] or has required an expensive reagent.[3] We wish to report an efficient solution to these problems as illustrated by the synthesis of progesterone (2) from dehydroepiandrosterone (3) using the phosphonate Wittig reaction.[4]

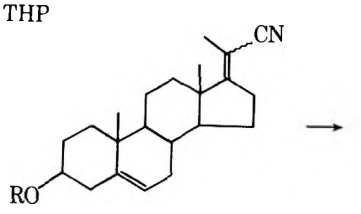
The condensation of the tetrahydropyranyl ether of dehydroepiandrosterone[5] (4) with the anion of 2-(diethylphosphono)-propionitrile (5) afforded the α,β-unsaturated nitrile (**6b**) in 77% yield as a mixture of *E* and *Z* isomers. The magnesium in methanol reduction[6] of **6b** provided the 17β-oriented side chain stereoselectively, and the subsequent hydrolysis of the tetrahydropyranyl protecting group furnished the hydroxynitrile **7** in 85% yield.[7] An alternative synthesis of **7** using pregnenolone and tosylmethyl isocyanide[8] afforded **7** in low yield.

The oxidation of **7** to the enone **8** using chromium reagents proceeded in low yield[9a] as a result of concomitant oxidation of **8** at C-6. The Oppenauer oxidation of **7** using aluminum isopropoxide and cyclohexanone[9b] circumvented this difficulty but presented the annoying problem of separating **8** from excess cyclohexanone[9b] by recrystallization or chromatography. Our inability to resolve this separation problem completely led us to substitute 4-methyl-1-piperidone (**9**) for cyclohexanone in the Oppenauer oxidation of **7**. This convenient modification of the Oppenauer oxidation afforded **8** in 90% yield following extraction of the acidified reaction mixture. As shown in Table I, this modification may prove useful in other small-scale oxidations of 3-hydroxy-Δ^5-steroids.

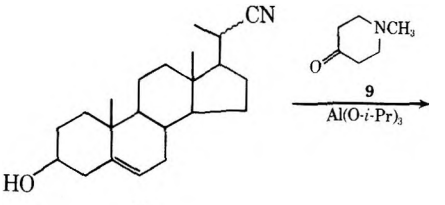
The ketalization of **8** with ethylene glycol furnished the ketal nitrile **10** in 62% yield. The oxidative decyanation[10] of **10** via the intermediate α-hydroperoxynitrile[11] **11** and the acid hydrolysis of the ethylene ketal protecting group furnished progesterone (**2**) in 69% yield. This synthesis illustrates a viable procedure for the introduction of a C-17β acetyl moiety



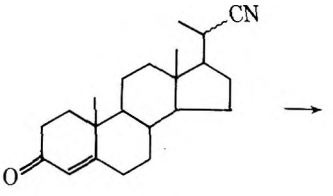
3, R = H
4, R = THP



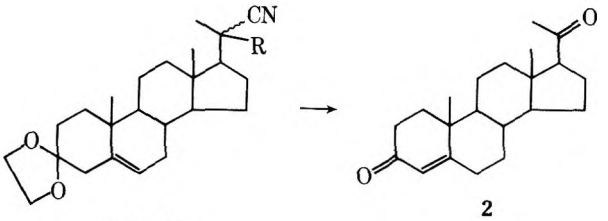
6a, R = H
b, R = THP



7



8



10, R = H
11, R = OOH

in steroids which (1) utilizes available or readily synthesized reagents and (2) is compatible with an isolated double bond elsewhere in the steroid.

Experimental Section

Infrared spectra were determined on a Perkin-Elmer Infracord spectrophotometer. NMR spectra were determined on a Varian A-60A spectrometer. Mass spectra were determined on a Varian MAT CH5 mass spectrometer. Melting points were determined using a Thomas-Hoover apparatus and are uncorrected.

2-(Diethylphosphono)-propionitrile (5). To 200 ml of thionyl chloride (2.8 mol, 1.4 equiv) under reflux was added 148 g (2.0 mol) of propionic acid dropwise over 0.5 h. The solution was refluxed for an additional 1 h. To the propionyl chloride solution was added 336 g (2.1 mol, 1.05 equiv) of bromine dropwise over 0.5 h. The dark red solution was refluxed for an additional 24 h.[12] To 1 l. of concentrated ammonium hydroxide at 0 °C in a 2-l. flask equipped with a Hirshberg stirrer was added the crude 2-bromopropionyl halide[13] solution dropwise over 1 h. The mixture was stirred for an additional 0.5 h at 0 °C, and the brown precipitate was collected in a large Buchner

Table I. Oppenauer Oxidation of Steroids Using Aluminum Isopropoxide and 1-Methyl-4-piperidone

Starting material	Product	Isolated yield, %
7	8	90
Pregnenolone	Progesterone	85
Cholesterol	Cholest-4-en-3-one	84
β-Sitosterol	24-Ethylcholest-4-en-3-one	71
Methyl 3β-hydroxy-5-cholenate	Methyl 3-keto 4-cholenate	67
3	Androst-4-ene-3,17-dione	81

funnel, washed with ca. 200 ml of water, and allowed to air dry. The crude product was recrystallized from reagent grade acetone[14] to afford 144 g (47%) of 2-bromopropionamide: mp 121–122.5 °C (lit.[15] mp 123 °C); ir ($CHCl_3$) 5.92 μ (C=O); NMR ($CDCl_3$) δ 2.02 (d, J = 7 Hz, 3, $CHCH_3$), 4.54 (q, J = 7 Hz, 1, $CHCH_3$), and 6.4 (broad s, 2, $CONH_2$).

A three-necked 500-ml round-bottomed flask equipped with a Hirshberg stirrer and connected to a high vacuum line via a dry ice–acetone trap was charged with 92.3 g (0.61 mol) of 2-bromopropionamide and 115 g (0.81 mol, 4.0 equiv) of phosphorus pentoxide. An oil bath at 180 °C was applied to the mixture. After approximately 10 min, the liquid was distilled into the trap under high vacuum. The liquid was subsequently distilled from ca. 1 g of phosphorus pentoxide to afford 49.7 g (61%) of 2-bromopropionitrile: bp 57.5–58.5 °C (25 mm) [lit.[16] 59 °C (24 mm)]; ir (TF) 4.55 μ (C≡N); NMR ($CDCl_3$) δ 2.00 (d, J = 7 Hz, 3, $CHCH_3$) and 4.40 (q, J = 7 Hz, 1, $CHCH_3$). In the same fashion, the above procedure was applied to other carboxylic acids to afford the α-bromo amides and α-bromonitriles in the following yields: butyric acid, 49, 76%; isovaleric acid, 31, 87%; octanoic acid, 36, 70%; and 3-phenylpropionic acid, 30, 44%.

A mixture of 74.5 g (0.56 mol) of 2-bromopropionitrile and 186 g (1.12 mol, 2.0 equiv) of triethyl phosphite was heated at 140–150 °C for 8.5 h under a slow stream of nitrogen. Ethyl bromide (95% yield) was collected in a dry ice–acetone trap. The product was distilled to afford 74.6 g (70%) of **5**: bp 103–107 °C (1.0 mm); ir (TF) 4.55 μ (C≡N); NMR ($CDCl_3$) δ 1.20–1.75 (m, 9, CH_2CH_3 and $CHCH_3$), 2.50–3.45 (m, 1, $CHCH_3$), and 3.90–4.50 (m, 4, CH_2CH_3).

20-Carbonitrile-3β-hydroxypregna-5,17(20)-diene Tetrahydropyranyl Ether (6b). To 120 mg (5.0 mmol) of sodium hydride in 8 ml of anhydrous DME[17] under a nitrogen atmosphere was added 955 mg (5.0 mmol) of **5** in 3 ml of DME. The mixture was refluxed for 10 min at which time gas evolution had ceased. To the white precipitate was added 372 mg (1 mmol) of **4** as a slurry in 4 ml of DME. The solution was refluxed for 24 h, cooled, and diluted with 50 ml of ether and 25 ml of cold water. The product was extracted with an additional 25 ml of ether. The combined ether solutions were washed consecutively with 25 ml of water and 25 ml of brine and dried over anhydrous $MgSO_4$. The solvent was evaporated, and the product was chromatographed on a 20 × 20 cm preparative layer Merck silica gel F254 plate in 1:1 ether–hexane.

A band (R_f 0.37) was eluted to afford 59 mg (16%) of unreacted **4**.

A band (R_f 0.47) was eluted to afford 315 mg (77%) of **6b**: ir ($CHCl_3$) 4.54 (C≡N) and 6.12 μ (C=C); NMR ($CDCl_3$) δ 0.94 and 1.03 (two s, 6, angular CH_3), 1.83 (broad s, 3, vinyl CH_3), 4.71 (m, 1, OCHO), 5.39 (m, 1, vinyl H); mass spectrum (70 eV) m/e (rel intensity) 308 (12, P − $C_5H_9O_2$), 307 (33), 105 (6), 91 (5), 86 (6), and 85 (100). The product is presumably a mixture of E and Z isomers as evidenced by the broad melting point (185–194 °C after three recrystallizations from ether).

Repetition of this reaction starting with 10 g of **4** afforded after column chromatography 7.9 g (72%) of **6b**.

In order to characterize **6b** further, 102 mg (0.25 mmol) of **6b** was hydrolyzed in 10 ml of methanol containing ca. 10 mg of p-toluenesulfonic acid monohydrate to afford 81 mg (100%) of 20-carbonitrile-3β-hydroxypregna-5,17(20)-diene (**6a**): mp 227–229 °C (lit.[18] mp 176–177 °C); ir ($CHCl_3$) 2.92 (OH), 4.52 (C≡N), 6.12 and 6.27 μ (C=C); NMR ($CDCl_3$) δ 0.95 and 1.03 (two s, 6, angular CH_3), 1.83 (broad s, 3, vinyl CH_3), and 5.39 (m, 1, vinyl H); mass spectrum (70 eV) m/e (rel intensity) 325 (54), 310 (17), 308 (20), 307 (72), 293 (16), 292 (60), 240 (13), 231 (11), 214 (37), 213 (58), and 105 (100). The discrepancy in melting points may reflect a different E/Z isomer ratio in **6a** prepared by two different routes.

20-Carbonitrile-3β-hydroxypregn-5-ene (7). The reduction[6] of 409 mg (1.0 mmol) of **6b** using 960 mg (40 mmol) of magnesium in 20 ml of methanol followed by hydrolysis with 30 ml of 6 N hydrochloric acid afforded, after recrystallizing twice from methanol and drying at 80 °C (0.2 mm), 277 mg (85%) of **7**: mp 170–173 °C; ir ($CHCl_3$) 4.49, 4.52 (C≡N), and 6.28 μ (C=C); NMR ($CDCl_3$) δ 0.76 and 1.03 (two s, 6, angular CH_3), 1.31 and 1.36 (two d, J = 7 Hz, 3, CH_3CH) and 5.37 (m, 1, vinyl H); mass spectrum (70 eV) m/e (rel intensity) 327 (43), 309 (42), 294 (39), 242 (27), 216 (39), 161 (38), and 119 (100).

20-Carbonitrilepregn-4-en-3-one (8). A solution of 327 mg (1.0 mmol) of **7** in 19 ml of toluene and 1 ml of 1-methyl-4-piperidone (**9**) was refluxed under a Dean-Stark trap until ca. 2 ml of distillate had collected. To the solution was added 306 mg (1.5 mmol) of aluminum isopropoxide. The mixture was refluxed for 6 h, cooled, diluted with 50 ml of ether, washed with two 25-ml portions of 1 M hydrochloric acid and 25 ml of brine, and dried over anhydrous $MgSO_4$. The product was chromatographed on two 20 × 20 cm preparative layer Merck silica gel F254 plates in ether to afford 294 mg (90%) of **8**: R_f 0.60; ir ($CHCl_3$) 4.49, 4.52 (C≡N), 6.01 (C=O), and 6.20 μ (C=C); NMR ($CDCl_3$) δ 0.80 and 1.22 (two s, 6, angular CH_3), 1.31 and 1.35 (two d, J = 7 Hz, 3, CH_3CH) and 5.76 (m, 1, vinyl H); mass spectrum (70 eV) m/e (rel intensity) 325 (84), 284 (91), 240 (29), 229 (14), 202 (17), 147 (25), 135 (25), and 124 (100).

20-Carbonitrilepregn-5-en-3-one Ethylene Ketal (10). A solution of 325 mg (1.0 mmol) of **8**, 310 mg (5.0 mmol) of ethylene glycol, and ca. 2 mg of p-toluenesulfonic acid monohydrate in 20 ml of benzene was refluxed under a Dean-Stark trap for 17 h. The product was diluted with 50 ml of ether, washed with 25 ml of saturated sodium bicarbonate solution and 25 ml of brine, and dried over anhydrous $MgSO_4$. The product was chromatographed on two 20 × 20 cm preparative layer Merck silica gel F254 plates in ether to afford 227 mg (62%) of **10**: R_f 0.85; ir ($CHCl_3$) 4.49 and 4.52 μ (C≡N); NMR ($CDCl_3$) δ 0.77 and 1.05 (two s, 6, angular CH_3), 1.31 and 1.36 (two d, J = 7 Hz, 3, CH_3CH), 3.96 (s, 4, OCH_2CH_2O), and 5.36 (m, 1, vinyl H); mass spectrum (70 eV) m/e (rel intensity) 369 (5), 341 (3), 100 (6), and 99 (100).

Progesterone (2). To a lithium diisopropylamide solution prepared from 111 mg (1.1 mmol) of diisopropylamine and 0.42 ml of 2.60 M n-butyllithium in 2.0 ml of hexane–THF at −78 °C under a nitrogen atmosphere was added 369 mg (1.0 mmol) of **10** in 2.0 ml of 50% hexamethylphosphoramide–THF. Dry oxygen gas was bubbled into the yellow solution (250 ml/min) at −78 °C for 30 min to afford a pale yellow solution which was quenched with 2 ml of 1 M sodium sulfite solution. The solution was stirred for 5 h at 25 °C, diluted with 25 ml of water, and extracted with 50 ml of 20% dichloromethane–ether. The product was washed with 25 ml of 1 M sodium hydroxide solution and 25 ml of brine and dried over anhydrous $MgSO_4$. To the crude white solid in 2 ml of THF was added 1.0 ml of glacial acetic acid and 0.5 ml of 1 M hydrochloric acid. The solution was stirred for 2.5 h, diluted with 25 ml of water, and extracted with 50 ml of 20% dichloromethane–ether. The product was washed with 25 ml of water, 25 ml of saturated sodium bicarbonate solution, and 25 ml of brine, and dried over anhydrous $MgSO_4$. The product was chromatographed on two 20 × 20 cm preparative layer Merck silica gel F254 plates in 10% dichloromethane–ether to afford 215 mg (69%) of **2** (R_f 0.54) which was identical with an authentic sample.

Acknowledgment. We wish to thank the Colorado Heart Association, the Research Corporation, the University of Colorado (Biomedical Sciences Support Grant), and the American Cancer Society (through the University of Colorado's Cancer Advisory Committee) for their generous financial support. We are also indebted to G. D. Searle and Co. for a generous gift of steroid precursors.

Registry No.—**2**, 57-83-0; **4**, 19637-35-5; **5**, 29668-61-9; (*E*)-**6a**, 58449-01-7; (*Z*)-**6a**, 58449-02-8; (*E*)-**6b**, 58449-03-9; (*Z*)-**6b**, 58449-04-0; **7** isomer 1, 58449-05-1; **7** isomer 2, 50303-63-4; **8**, 58462-91-2; **9**, 1445-73-4; **10**, 58462-92-3; 2-bromopropionamide, 5875-25-2; phosphorus pentoxide, 1314-56-3; 2-bromopropionitrile, 19481-82-4; triethyl phosphite, 122-52-1; ethylene glycol, 107-21-1; lithium diisopropylamide, 4111-54-0.

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(7) The hydroxynitrile **7** was a mixture of diastereomers (at C-20) as evidenced by the NMR and ir spectra.

(8) O. H. Oldenziel and A. M. van Leusen, *Tetrahedron Lett.*, 1357 (1973). The low yield was, in part, the result of the extensive purification necessary to free **7** from unreacted pregnenolone.
(9) (a) For example, the yield of **8** using Jones reagent was 39% and using Collins reagent was 56%. (b) The use of a volatile ketone such as acetone required long reaction times and furnished **8** in low yield (44% after 60 h).
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(12) E. Schwenk and D. Papa, *J. Am. Chem. Soc.*, **70**, 3626 (1948).
(13) Distillation of the product at this stage afforded a mixture of 2-bromopropionyl chloride and bromide.
(14) Filtration of the hot acetone solution was often necessary in order to remove small amounts of ammonium salts.
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Synthesis of 1,4-Disubstituted Tetrazoline-5-thiones

Gerrit L'abbé,* Guido Vermeulen, Jacques Flémal, and Suzanne Toppet

Department of Chemistry, University of Leuven, Celestijnenlaan 200F, 3030 Heverlee, Belgium

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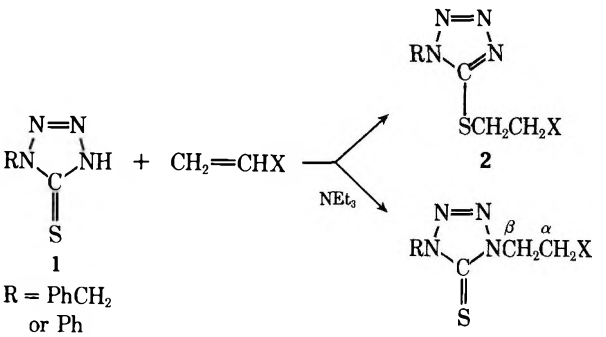
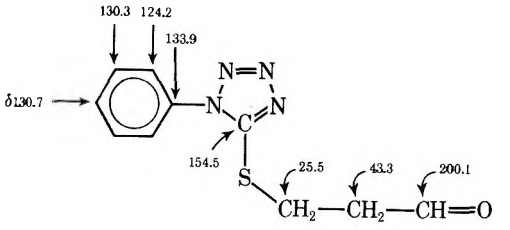
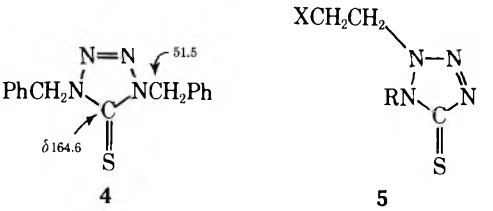
1,4-Disubstituted tetrazoline-5-thiones (**3**) may be considered as potential precursors for the hitherto unknown diaziridinethiones[1] which are of current interest in our laboratory.[2] We have already reported that alkylation, acylation, and sulfonylation of 1-benzyl-4*H*-tetrazoline-5-thione (**1**, R = $PhCH_2$) in the presence of triethylamine resulted in S-substitution in all cases except with phenylacetyl chloride, which furnished the N derivative.[3] Sulfenylations of 1-substituted 4*H*-tetrazoline-5-thiones in the presence of pyridine also occurred at sulfur as was shown by Stajer et al.[4]

Very recently, Lippmann and Reifegerste[5] carried out Michael additions of 1-phenyl-4*H*-tetrazoline-5-thione onto α,β-unsaturated aldehydes, maleic anhydride, and methyl acrylate in the absence of base and concluded (correctly) from their ^1H NMR spectra that S-addition products (**2**) were formed. Independently, we have carried out Michael additions with 1-benzyl- (or phenyl-) 4*H*-tetrazoline-5-thione (**1**) under slightly modified experimental conditions (THF/NEt_3) which resulted in the formation of N derivatives (**3**) in all cases (see Table I). The structures of **3a–f** are fully supported by the ^{13}C NMR data recorded in Table II. That N-addition occurred instead of S-addition is apparent from the absorptions at δ 164 and 42–44 ppm which are attributed to the C=S and the β-CH_2 carbon atoms. If addition would have occurred at sulfur to give **2**, the C=N and β-CH_2 carbon resonances would be found at δ 154 and 25 ppm, respectively. This is shown below for structure **2a** prepared by the method of Lippmann and Reifegerste.[5] The assignment of the absorption peak at δ 164





ppm to the C=S carbon atom[3] is confirmed by the ^{13}C NMR spectrum of 1,4-dibenzyltetrazoline-5-thione (**4**) (C=S at δ 164.6 ppm). This compound was obtained in our laboratory



from the corresponding ketone[6] upon treatment with P_2S_5. Thus far, we have only interpreted our results in terms of S vs. N_4 addition. The alternative structure for the N adduct, namely **5**, can be excluded on the basis of the position of the ortho phenyl carbon absorption in compounds **3a,c,e**. According to Begtrup[7] the chemical shift value of this ortho carbon atom is strongly dependent on the extent of interannular conjugation between the two rings, resulting in a downfield shift as the steric hindrance increases. This is illustrated for three compounds, **6**, **7**, and **8**, taken from the work of Begtrup.[7] In our phenyl substituted compounds **3a,c,e** (as well as in **2a**) the ortho phenyl carbon absorptions are found at ca. δ 124 ppm in accordance with the value noted on model compound **7** which has only one neighboring sub-

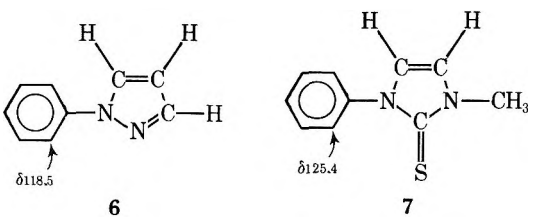


Table I. 1,4-Disubstituted Tetrazoline-5-thiones

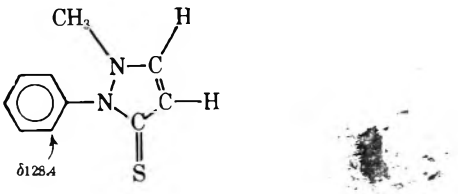
Compd	R	X	Yield, %	^1H NMR, δ values[a] $PhCH_2N$	NCH_2CH_2X	X
3a	Ph	CHO	43		4.60, 3.18	9.84
3b	$PhCH_2$	COMe	85	5.38	4.45, 3.07	2.14
3c	Ph	COMe	76		4.56, 3.18	2.24
3d	$PhCH_2$	CO_2Me	70	5.56	4.56, 2.92	3.61
3e	Ph	CO_2Me	57		4.70, 3.10	3.70
3f	$PhCH_2$	CN	72.5	5.43	4.50, 2.98	

[a] All the spectra were recorded in $CDCl_3$ with Me_4Si as internal reference. The aromatic proton absorptions are omitted.

Table II. ^{13}C Chemical Shifts[a] for the Michael Adducts 3

Compd	C=S	NCH_2CH_2X	Other shift values
3a	163.7	42.1, 40.9	CHO at 198.6
3b	164.2	43.2, 40.2	$COCH_3$ at 204.9 and 29.9
3c	163.6	43.3, 40.2	$COCH_3$ at 205 and 30
3d	164.4	44, 31.7	CO_2CH_3 at 170.5 and 52
3e	163.6	44, 31.7	CO_2CH_3 at 170.6 and 52.2
3f	164.4	43.6, 16.3	CN at 116.4

[a] All the spectra were recorded in $CDCl_3$ with Me_4Si as internal reference. The benzyl methylene carbons in **3b,d,f** absorbed at 51.1–51.4 ppm. For compounds **3a,c,e** the phenyl carbon atoms resonated at 135.1, 124 (ortho), 129.6 (meta), and 130 ppm (para).



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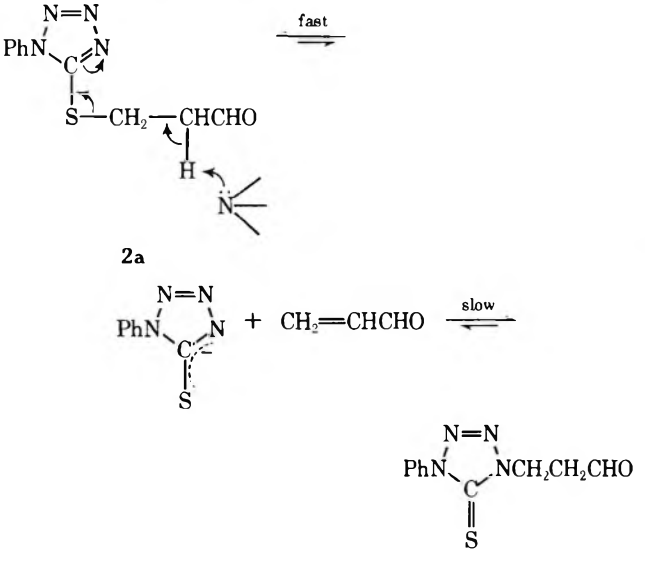
stituent. For compound **5** (R = Ph), the two substituents adjacent to the phenyl group would impede interannular conjugation to such an extent that a chemical shift of about δ 128 ppm would be expected for the carbon atom under discussion (see model 8).

From the mechanistic point of view, it is worth mentioning that **2a** isomerizes into **3a** when heated at 70 °C for 1 h in the presence of 1,4-diazabicyclo[2.2.2]octane (Dabco, monitored by NMR in $CDCl_3$). In the absence of base, no isomerization occurred at 70 °C within 1 h, whereas 20% conversion into **3a** was observed at room temperature after a period of 2 months. When the reaction of 1-phenyl-4*H*-tetrazoline-5-thione and acrolein in the presence of Dabco was followed by NMR ($CDCl_3$ as solvent), the S derivative **2a** (triplet at δ 3.5 for the β-CH_2) was formed first, but underwent further isomerization into the N derivative **3a** (triplet at δ 4.6 for the β-CH_2). A mechanism which accounts for the amine-catalyzed isomerization of **2a** into **3a** is given below.[8]



In conclusion, the Michael additions of 1-substituted 4*H*-tetrazoline-5-thiones **1** onto electrophilic olefins can be carried out either under kinetic or thermodynamic controlled conditions. Until now the 1,4-disubstituted tetrazoline-5-thiones **3** could not be transformed into diaziridinethiones. They remained unchanged when heated at 120–150 °C for 2 days (monitored by ir), thereby resembling the corresponding ketones[6,9] in their thermal stability. Also photolysis did not produce the three-membered ring but, instead, furnished a carbodiimide after loss of nitrogen and sulfur.[10]

Experimental Section

The starting materials **1** (R = $PhCH_2$, mp 144 °C; R = Ph, mp 151 °C) were prepared by the procedure of Lieber and Ramachandran.[11] Adduct **2a** (oil) was synthesized in 41% yield by the method of Lippmann and Reifegerste.[5] The ^{13}C NMR spectra were taken with a XL-100 spectrometer equipped with a device for pulsed Fourier transform operation.

General Procedure for the Synthesis of 1,4-Disubstituted Tetrazoline-5-thiones. Compound **1** (0.03 mol) was allowed to react with 2 equiv of olefin and 1 equiv of triethylamine in dry THF (100 ml) at reflux temperature (ca. 80 °C) for the appropriate reaction time. The solvent (including Et_3N and the excess of olefin) was removed in vacuo and the residue was chromatographed on silica gel using CCl_4–EtOAc as the eluent. Compound **3a** was obtained as a colorless oil, reaction time 1 h, ir (neat) 1717 cm^{-1}. Anal. Calcd for $M^{\cdot+}$ (determined by high-resolution exact-mass measurements): 234.05748. Found: 234.05654.

Compound **3b** was obtained as a colorless, viscous oil, reaction time 1 day, ir (neat) 1720 cm^{-1}. Anal. Calcd for $M^{\cdot+}$: 262.08828. Found: 262.08744. Compound **3c** was obtained from the reaction residue by crystallization from CCl_4, mp 73–74 °C, reaction time 3 days, ir (KBr) 1700 cm^{-1}. Anal. Calcd for $M^{\cdot+}$: 248.07317. Found: 248.07238.

Compound **3d** was obtained as a colorless, viscous oil, reaction time 3 weeks, ir (neat) 1730 cm^{-1}. Anal. Calcd for $M^{\cdot+}$: 278.08374. Found: 278.08175.

Compound **3e** was obtained as a viscous oil, reaction time 16 days, ir (neat) 1735 cm^{-1}. Anal. Calcd for $M^{\cdot+}$: 264.06808. Found: 264.06785.

Compound **3f** was obtained as white needles, mp 59 °C (ether–*n*-hexane), reaction time 3 weeks, ir (KBr) 2255 cm^{-1}. Anal. Calcd for $M^{\cdot+}$: 245.07351. Found: 245.07262.

Synthesis of 1,4-Dibenzyltetrazoline-5-thione (4). 1,4-Dibenzyltetrazolinone (1 g)[6] and P_2S_5 (2 g) were heated in dry toluene (10 ml) at reflux temperature for 2 days. After addition of 50 ml of CCl_4, the reaction mixture was filtered and the filtrate was chromatographed on silica gel using CCl_4–1.5% EtOAc as the eluent. Compound **4** was obtained in 57% yield and was crystallized from ether–petroleum ether to give white needles: mp 109–109.5 °C; ^1H NMR ($CDCl_3$) δ 5.38 (s, 4 H) and 7.2–7.5 (m, 10 H). Anal. Calcd for $M^{\cdot+}$ (determined by high-resolution exact-mass measurements): 282.09391. Found: 282.09386.

Registry No.—**1** (R = $PhCH_2$), 33898-72-5; **1** (R = Ph), 86-93-1; **3a**, 58408-31-4; **3b**, 58408-32-5; **3c**, 58408-33-6; **3d**, 58408-34-7; **3e**, 58438-25-8; **3f**, 58408-35-8; **4**, 58408-36-9; P_2S_5, 1314-80-3; 1,4-dibenzyltetrazolinone, 20628-50-6; acrolein, 107-02-8; methyl vinyl ketone, 78-93-3; methyl acrylate, 96-33-3; acrylonitrile, 107-12-0.

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Direct Synthesis of Indole by the Fischer Indole Synthesis

Masao Nakazaki* and Koji Yamamoto

Department of Chemistry, Faculty of Engineering Science, Osaka University, Toyonaka, Osaka, Japan

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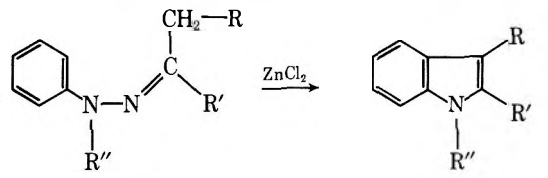
The Fischer indole synthesis has been regarded as the most versatile method for the preparation of indoles. Oddly enough, however, indole (**2a**) itself has not been prepared directly from acetaldehyde phenylhydrazone (**1a**) by the Fischer indole synthesis. Since 1886 when Fischer[1] stated "all trials to obtain indole itself by means of zinc chloride have been so far fruitless", various Lewis acids have been employed only to find complete failure.[2]

Recently, two research groups[3,4] claimed the successful preparation of indole (**2a**) from **1a** using modified alumina catalysts. In this paper we report the first direct synthesis of indole from **1a** by means of zinc chloride (Scheme I), the catalyst originally introduced by Fischer.

Scheme I



1a, R = R′ = R″ = H
b, R = Me; R′ = R″ = H
c, R = R″ = H; R′ = Me
d, R = R′ = H; R″ = Me

2a, R = R′ = R″ = H
b, R = Me; R′ = R″ = H
c, R = R″ = H; R′ = Me
d, R = R′ = H; R″ = Me

Absence of the alkyl group (R) in **1a** should shift the hydrazone–enehydrazine equilibrium[2] away from the enehydrazine form which is necessary for the indolization of **1a**. However, the vulnerability of indole (**2a**) to condensation with the unreacted hydrazone under drastic conditions was thought to be mainly responsible for this notable exception to the Fischer indole synthesis. Thus we assume that Fischer and his successors, using various catalysts, must have had indole in their reaction mixtures, but failed to isolate it because of its fleeting existence. To overcome this difficulty, we used a flow method, with a stream of carrier gas to remove the indole from the contact catalyst immediately after its formation.

Acetaldehyde phenylhydrazone (**1a**) was passed by a stream of nitrogen through a heated combustion tube (290–300 °C) packed with porous glass beads coated with zinc chloride. From the reaction mixture, a 36% yield of indole (**2a**) together with aniline (46%) was isolated. Vapor phase chromatography of the reaction mixture revealed the formation of acetonitrile (10%).

A control experiment without zinc chloride afforded a mixture of aniline and acetonitrile with a trace of indole (**2a**) whose presence was detected by thin layer chromatography.

Application of this method to propionaldehyde and acetone phenylhydrazone (**1b, 1c**) gave respectively skatole (**2b**) (70%) and 2-methylindole (**2c**) (79%) in good yields, but acetaldehyde 1-methylphenylhydrazone (**1d**) afforded *N*-methylindole (**2d**) in rather low yield (27%).

It is pertinent to note here a rather surprising observation that the vapor phase chromatography of acetaldehyde phenylhydrazone (**1a**) exhibited the peaks corresponding to acetonitrile, aniline, and indole (**2a**); undoubtedly indolization occurs in the metallic injection chamber (250 °C). Formation of the indoles **2b, 2c,** and **2d** from the corresponding phenylhydrazones **1b, 1c,** and **1d** was also observed on vapor phase chromatography.

Experimental Section

Melting points and boiling points were uncorrected. Vapor phase chromatography (VPC) was carried out using a JEOL JGC-20K gas chromatograph equipped with a 2-m stainless steel column packed with 5% SE-30 (134 °C) on Chromosorb W for indoles, and a 2-m column with 10% PEG-20M (60 °C) for acetonitrile.

Thin layer chromatography (TLC) employed silica gel G as the support, benzene as the developer, and iodine for detection.

Elemental analyses were performed with a Yanagimoto CHN-Corder Type II. All indoles and their derivatives were identified by comparison with authentic samples.

General Procedure. The apparatus consisted of a reaction tube, 700 mm long and 17 mm in diameter, provided with an inlet tube for the carrier gas and a side arm to which a graduated dropping funnel was connected. The tube was supported in an electrically heated furnace and the lower end of the tube was fitted with a receiver cooled in a dry ice–acetone bath.

The catalyst was prepared by evaporation (in vacuo) of the solvent from a mixture of 2 g of zinc chloride, 20 ml of ethanol, and 34 g of porous glass beads (3 mm diameter). The reaction tube was packed with the catalyst held in place by a glass wool, and was heated to 290–300 °C.

A solution of phenylhydrazone in benzene was introduced from the dropping funnel with a stream of nitrogen (150 ml/min) over 60–80 min. An additional 20 ml of benzene was introduced and the reaction tube was swept with the carrier gas for a further 30 min.

Indole (2a). A solution of 10 g of **1a,** bp 94–96 °C (2 mm), in 20 ml of benzene was introduced in the reaction tube. The product collected in the receiver was analyzed by VPC which showed the presence of indole (**2a**), aniline, and acetonitrile in a ratio of 4:6:1. The reaction product was diluted with ether and extracted with 3% hydrochloric acid. After washing with 3% sodium bicarbonate solution and drying over anhydrous sodium sulfate, the solvent was removed from the ethereal solution to give 3.1 g (36%) of indole (**2a**), which was recrystallized from petroleum ether, mp 52–53 °C (lit.[5] mp 52 °C).

Thy hydrochloric acid extract was made basic with 10% sodium hydroxide solution and extracted with ether. Evaporation of the solvent gave 3.2 g (46%) of aniline, which was identified by conversion into acetanilide, mp 113–114 °C (from ethanol–water).

Starting from a solution of phenylhydrazine (4 g) and paraldehyde (1.6 g) in 10 ml of benzene, **2a** (1.5 g, 36%) and aniline (2.0 g, 56%) were isolated following the same procedure described above.

Skatole (2b). Starting from a solution of 4.6 g of **1b,** bp 105–108 °C (2 mm), in benzene (10 ml), the general procedure furnished skatole (**2b,** 1.8 g, 70%) and aniline (1.1 g, 28%). After recrystallization from ligroin, **2b** melted at 89–91 °C (lit.[6] mp 96 °C).

2-Methylindole (2c). VPC analysis of the reaction product from a solution of 2 g of **1c,** bp 105–108 °C (2 mm), in benzene (4 ml) showed the presence of 2-methylindole (**2c**) and aniline in a ratio of 9:1. From the reaction mixture was isolated 1.4 g of **2c** (79%), mp 58–60 °C (from ethanol–water) (lit.[1] mp 60 °C).

***N*-Methylindole (2d).** The reaction mixture from a solution of 4.6 g of **1d,** bp 105–108 °C (2 mm), in benzene (10 ml) gave 1.1 g (27%) of *N*-methylindole, bp 103–105 °C (2 mm), and 1.4 g (42%) of *N*-methylaniline, bp 121–123 °C (80 mm).

The picrate of **2d** had mp 148–149 °C (from ethanol) (lit.[7] mp 150 °C).

The general procedure starting from a solution of paraldehyde (2 g) and 1-methylphenylhydrazine (5 g) in 15 ml of benzene also afforded *N*-methylindole (**2d,** 1.4 g, 23%) and *N*-methylaniline (19 g, 39%).

Registry No.—**1a,** 935-07-9; **1b,** 7423-16-7; **1c,** 103-02-6; **1d,** 5311-88-6; **2a,** 120-72-9; **2b,** 83-34-1; **2c,** 95-20-5; **2d,** 603-76-9; **2d** picrate, 29052-34-4.

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Carbon-13 Nuclear Magnetic Resonance Analysis of Vobasine-Like Indole Alkaloids[1]

Alain Ahond, Anne-Marie Bui, and Pierre Potier

Institut de Chimie des Substances Naturelles, Centre National de la Recherche Scientifique, 91190 Gif-sur-Yvette, France

Edward W. Hagaman and Ernest Wenkert*[2]

Department of Chemistry, Indiana University, Bloomington, Indiana 47401

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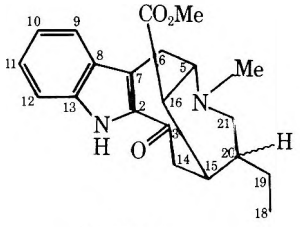
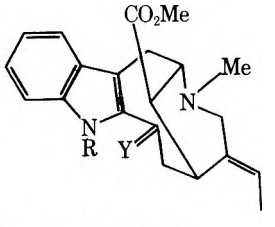
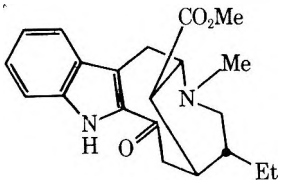
In continuation of a ^{13}C NMR study of indole alkaloids of various structure types[3] an analysis of selected samples of the α-acylindole family was undertaken. Aside from determining the basic carbon shifts of this alkaloid group—dregamine (**1a**), tabernaemontanine (**1b**), vobasine (**2a**), ochropamine (**2b**), and their derivatives 16-epidregamine (**3**), vobasinol (**2c**), and vobasinyl acetate (**2d**)—it was of interest to ascertain by direct analysis the C(20) stereochemistry of **1a** and **1b**[4] and to discover whether the strong anisotropic shielding of the methoxy protons of the alkaloids by the proximate indole ring[5] is reflected by any carbon shift perturbation of the ester function.



1a, 20β-H
b, 20α-H



2a, R = H; Y = O
b, R = Me; Y = O
c, R = H; Y = α-H, β-OH
d, R = H; Y = α-H, β-OAc



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Inspection of the ^{13}C NMR spectra of the indolic compounds led to the chemical shifts depicted in Table I. The shift assignment is facilitated by the strong dissimilarity of most carbons from each other, when both the field position and multiplicity of their signals is utilized, and limited only to the differentiation of the methylene and nonaromatic methine resonances. The aminomethylene and α-ketomethylene signals are downfield of those of the other methylenes. Epimerization of C(16) with accompanying α-keto deuteration distinguishes C(14) from C(21) in dregamine (**1a**) and its 16 epimer (**3**). The same low-field methylene pair in tabernaemontanine (**1b**) is differentiated by C(21) deuteration of 20,21-didehydrotabernaemontanine.[6] The upfield pair of methylene signals of **1a**, **1b**, and **3** belong to C(6) and C(19) whose hydrogens occupy separate field positions. As a consequence the carbon–hydrogen, one-bond coupling characteristics of these signals in single-frequency, off-resonance decoupled (sford) spectra permit their allocation. The double bond of vobasine (**2a**) and its relatives (**2**) reduces C(6) to being the only upfield methylene, while comparison of vobasine-like compounds of different C(3) oxidation level with each other distinguishes C(14) from C(21) in these substances.

The aminomethine, C(5), possesses the lowest field methine signal of all substances. The next lowest field methine signal, that of C(16), exhibits sharp one-bond coupling components in its sford spectra in contrast to all other methine signals and characteristic of few long-range carbon–hydrogen interactions and no second-order couplings. This criterion is of special significance in the differentiation of C(16) from C(20) of **1b** in view of the shift similarity of these carbon centers. Only one methine remains in vobasine (**2a**) and its relatives (**2**), whose shift serves as a model δ value for C(15) in compounds **1** and **3**. Carbon 15 in **1a** was identified also by the observation of a 3-Hz β-deuterium substitution effect exerted by the three deuteriums in 14,14,16-trideuteriodregamine.

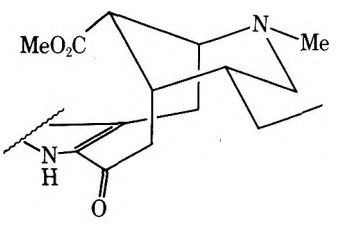
Conversion of the equatorial state of the carbomethoxy group within the piperidine ring of dregamine (**1a**) into the axial form, i.e., into 16-epidregamine (**3**), causes ca. 5 ppm

Table I. Carbon Shifts of α-Acylindole Alkaloids and Their Derivatives[a]

	1a	1b	3	2a	2b[b]	2c[c]	2d[c,d]
C(2)	133.8	133.7	135.0	133.8	133.3	135.4	133.7
C(3)	190.7	190.5	192.5	189.9	190.7	66.8	68.3
C(5)	56.5	56.7	55.4	57.0	57.0	59.4	60.8
C(6)	20.1	18.4	19.4	20.2	21.0	19.6	18.3
C(7)	120.1	120.5	121.1	119.9	120.7	107.3	108.7
C(8)	128.8	128.3	128.3	128.0	126.6	128.7	128.2
C(9)	120.5[e]	120.5[e]	120.8[e]	120.3[e]	120.2[e]	117.6	117.6
C(10)	120.0[e]	119.9[e]	120.5[e]	119.9[e]	119.8[e]	118.6	118.9
C(11)	126.3	126.3	126.9	126.2	125.8	121.4	121.2
C(12)	111.8	111.7	112.4	111.8	109.5	110.0	110.6
C(13)	136.4	136.4	136.7	136.4[f]	138.7	136.7[e]	136.2
C(14)	39.1	45.4	38.9	42.8	45.4	35.5	36.0
C(15)	30.5	31.7	29.5	30.5	30.6	29.2	30.1
C(16)	48.8	43.3	44.3	46.2	46.5	47.1	44.5
C(18)	11.3	12.6	11.4	12.0	12.1	12.2	12.3
C(19)	23.3	25.3	23.5	120.0[e]	119.8	118.6	120.9
C(20)	43.2	42.4	38.0	135.8[f]	135.7	136.5[e]	134.9
C(21)	48.5	46.4	48.6	51.5	51.8	53.9	53.9
C=O	170.9	171.6	173.9	170.9	170.9	174.3	170.0
OMe	50.1	50.1	51.8	50.1	49.8	50.3	49.8
NMe	42.3	42.9	42.6	42.2	42.2	42.1	42.0

[a] In parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] $\delta(N_a\text{-Me}) = 32.8$ ppm. [c] The indole carbon resonances are based on those of R. G. Parker and J. D. Roberts [*J. Org. Chem.*, **35**, 996 (1970)] as corrected by G. W. Gribble, R. B. Nelson, J. L. Johnson, and G. C. Levy, *J. Org. Chem.*, **40**, 3720 (1975). [d] The acetyl δ(Me) and δ(CO) values are 21.0 and 169.4 ppm, respectively. [e,f] Signals bearing the same superscript within any vertical column may be reversed.

shielding on C(20). This γ effect is possible only in the presence of an axial H(20) and constrains the ethyl group to an equatorial orientation, as illustrated in partial structures **4** and **5**, respectively. As a consequence, tabernaemontanine (**1b**) must possess an axial ethyl function (**6**). This is confirmed by the loss and gain of γ effects in **1b** relative to **1a** at C(14) and C(16), respectively. Furthermore, the chemical shift of the methyl component of the ethyl group reflects the conformation of the two-carbon side chain.[7]



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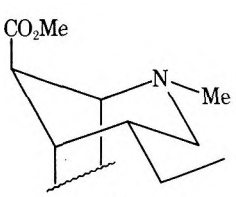

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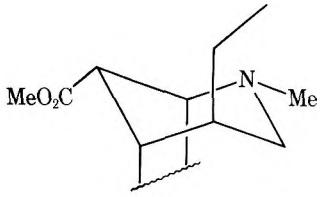

6

While the shifts of the carbomethoxy group of 16-epidregamine (**3, 5**) are characteristic of methyl cyclohexanecarboxylates,[3b,8] the carbonyl and methoxy groups of compounds **1, 2a,** and **2b** are shielded anomalously by 2.7 ± 0.4 and 1.8 ± 0.2 ppm, respectively. These shift perturbations reflect the close proximity of the carbomethoxy group in substances **1** and **2** to the α-acylindole moiety and are diagnostic of the C(16) stereochemistry. The indole α carbon and neighboring keto carbon respond likewise by being shielded by 1.2 ± 0.1 and 2.0 ± 0.1 ppm, respectively. Since strong anisotropic shielding (0.89 ppm) of the methoxy hydrogens of vobasine (**2a**), relative to 16-isovobasine, by the indole ring was observed some time ago,[5] the shift perturbation of the methoxy carbon may be due to the same effect. Anisotropic shielding of carbon centers has been predicted to be comparable in magnitude to such shielding observed in ^{1}H NMR spectroscopy[9] and therefore has been difficult to isolate as a unique contribution to the chemical shift.[10]

The methyl ester carbonyl shift of vobasinyl acetate (**2d**) is similar to that of the 3-keto systems **1, 2a,** and **2b,** while that of vobasinol (**2c**) is downfield 4.3 ppm owing to hydrogen bonding with the 3β-hydroxy group.[8]

Conjugation of a carbonyl group with the indole ring through its α carbon causes shift alteration throughout the aromatic system. The strong deshielding of the customarily high-field indole β carbon[3,11] is especially characteristic of the α-acyl attachment.

Experimental Section

The ^{13}C NMR spectra were recorded on Bruker HX90E and Varian XL-100-15 spectrometers operating at 22.6 and 25.2 MHz in the Fourier transform mode, respectively. The shifts indicated on formula i are from a deuteriochloroform solution [$\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm] and the stars thereon represent interchangeable signals.

Acknowledgment. The authors express their sincere thanks to Aline and Henri-Philippe Husson for the preparation of 21-deuteriotabernaemontanine, Abbas Shafiee for the deuterated derivatives of **1a** and **3**, Pierre Mangeney and Yves Langlois for a sample of i, and Jean-Pierre Cosson and B. C. Das for a sample of **2b**.

Registry No.—**1a,** 2299-26-5; **1b,** 2134-98-7; **2a,** 2134-83-0; **2b,** 2134-97-6; **2c,** 7168-77-6; **2d,** 58324-78-0; **3,** 52389-31-8.

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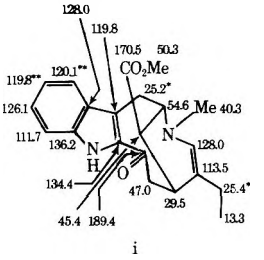
(1) (a) Etudes en Série Indolique. VII. For the previous paper see A. Husson, Y. Langlois, C. Riche, H.-P. Husson, and P. Potier, *Tetrahedron*, **29,** 3095 (1973). (b) Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances. XL. For the previous publication see E. Wenkert and E. W. Hagaman, *J. Org. Chem.*, **41,** 701 (1976).
(2) Address correspondence to Department of Chemistry, Rice University, Houston, Texas 77001.
(3) (a) M. C. Koch, M. M. Plat, N. Préaux, H. E. Gottlieb, E. W. Hagaman, F. M. Schell, and E. Wenkert, *J. Org. Chem.*, **40,** 2836 (1975); (b) E. Wenkert, C.-J. Chang, H. P. S. Chawla, D. W. Cochran, E. W. Hagaman, J. C. King, and K. Orito, *J. Am. Chem. Soc.*, in press; and preceding papers.
(4) The recent conversion of tabernaemontanine (**1b**) into ervatamine and the latter's x-ray analysis[1a] indicated the necessity of the revision of the alkaloid's heretofore accepted stereostructure [U. Renner, D. A. Prins, A. L. Burlingame, and K. Biemann, *Helv. Chim. Acta*, **46,** 2186 (1963)].
(5) M. P. Cava, S. K. Talapatra, J. A. Weisbach, B. Douglas, and G. O. Dudek, *Tetrahedron Lett.*, 53 (1963).
(6) The carbon shifts of this substance are delineated on formula i.



i

(7) The ca. 1 ppm difference of C(18) shifts has been shown earlier to be diagnostic of the C(20) stereochemistry in corynantheoid alkaloids.[3a]
(8) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972.
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(10) Cf., inter alia, H. Günther, H. Schmickler, H. Königshofen, K. Recker, and E. Vogel, *Angew. Chem., Int. Ed. Engl.*, **12,** 243 (1973); R. H. Levin and J. D. Roberts, *Tetrahedron Lett.*, 135 (1973).
(11) Cf. R. J. Sundberg and F. X. Smith, *J. Org. Chem.*, **40,** 2613 (1975).

A Convenient Method for Estimation of Alkyllithium Concentrations

William G. Kofron* and Leona M. Baclawski

Department of Chemistry, The University of Akron, Akron, Ohio 44325

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Alkyllithium reagents have become increasingly important in organic synthesis. Commercial alkyllithium reagents are usually accompanied with a lot analysis, but often even freshly obtained solutions have obviously deteriorated, being dark colored and cloudy, and most alkyllithium solutions deteriorate after the container is opened. For use in metalation reactions and alkylations, an excess or a deficiency of alkyllithium is often detrimental, especially where dilithio intermediates are formed.[1] Thus analysis of an alkyllithium reagent is often desirable.

The standard procedure for such an analysis requires a double titration—total alkali, which includes the alkyllithium and such species as alkoxides formed by reaction of the reagent with air, from which is subtracted that portion which does not react rapidly with certain halides. The method is said not to be useful for certain alkyllithium reagents.[2]

Since the organolithium compound is so often used for metalation, we offer a convenient method of analysis which is based on the reaction for which the reagent is intended, namely carbon lithiation, and which produces a color at the end point and is thus independent of indicator. A similar acid–indicator system has been proposed; however, solvent plays a critical role, and there is some difference from the values determined by the double titration procedure.[3]

We noticed in the metalation of certain pyridine esters that the red dianion color was not observed until the butyllithium

Table I. Standardization of Alkyllithium Solutions[a]

Sample	Label	Method	Concn
BuLi[b]	1.6 M	$(C_6H_5)_2CHCOOH$	1.47
		Double titration	1.48
BuLi[c]	1.66 M	$(C_6H_5)_2CHCOOH$	1.12
		Double titration	1.14
CH_3Li[d]	1.56 M	$(C_6H_5)_2CHCOOH$	1.06
		Double titration[e]	1.12
CH_3Li[f]	2.1 M	$(C_6H_5)_2CHCOOH$	1.78
		Double titration	1.80

[a] At least two determinations in agreement. [b] The bottle had previously been opened but there was no discoloration or sediment. [c] The bottle had previously been opened, there was much sediment, and the solution was dark brown. [d] The bottle had previously been opened and there was much sediment. [e] The double titration is said not to be useful for methyllithium when benzyl chloride is used; we used dibromoethane in all our double titrations. [f] The bottle had not previously been opened.

was considerably in excess of that calculated (from the lot analysis) for complete formation of the yellow monoanion.[4] Careful standardization of the butyllithium indicated a low titer. However if the lot analysis was ignored, the volume of a molar equivalent was indicated by initial formation of the red dianion color, and it was sufficient to add a second equal volume to form the dianion completely.

$$\underset{\text{(yellow)}}{H\text{-}P\text{-}H} \rightarrow \underset{\text{(red)}}{H\text{-}P\text{-}Li} \rightarrow Li\text{-}P\text{-}Li$$

The involved synthesis of the pyridine ester precludes its widespread use for this purpose,[5] but many compounds produce dianions differently colored from the monoanion, and one of these, cheap and readily available, is proposed.

Diphenylacetic acid has the advantage of being a solid, stable on storage and easily weighed. A sample of diphenylacetic acid (typically 0.50 g) is weighed into an Erlenmeyer flask and dissolved in tetrahydrofuran (10 ml), and the alkyllithium solution is run in from a syringe until the yellow end point is reached. The yellow color indicates formation of lithium α-lithiodiphenylacetate after all the carboxyl proton is consumed.

$$(C_6H_5)_2CHCOOH \rightarrow \underset{\text{(colorless)}}{(C_6H_5)_2CHCOO^-Li^+} \rightarrow \underset{\text{(yellow)}}{(C_6H_5)_2CLiCOO^-Li^+}$$

Table I summarizes results from several commercial samples of alkyllithium reagents.

Registry No.—BuLi, 109-72-8; CH_3Li, 917-54-4; $(C_6H_5)_2CHCOOH$, 117-34-0.

References and Notes

(1) See, for example, W. G. Kofron and M. K. Yeh, *J. Org. Chem.*, **41**, 438 (1976).
(2) See T. R. Crompton, "Chemical Analysis of Organometallic Compounds", Vol. 1, Academic Press, New York, N.Y., 1973, Chapter 1.
(3) R. L. Eppley and J. A. Dixon, *J. Organomet. Chem.*, **8**, 176 (1967).
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Carbon-13–Proton Long-Range Couplings of Phenols Hydrogen Bonding and Stereospecificity[1]

Summary: The long-range $^{13}C-^{1}H$ coupling constants of phenol and its ortho-substituted derivatives (salicylaldehyde, salicylic acid, methyl salicylate, and o-hydroxyacetophenone) and the stereospecific effect of the intramolecular hydrogen bonding on the long-range couplings are studied.

Sir: The analysis of carbon-13 magnetic resonance (^{13}C NMR) spectra of aromatic molecules has traditionally been accomplished on the basis of the additivity principle. But the effects of individual substituents (shielding constants) are not always additive, particularly for ortho-substituted compounds.[2] This usually leaves some uncertainty in the assignments, which has previously been overcome by other means.[1-4] However, a better approach to solve this problem is the full utilization of $^{13}C-^{1}H$ coupling patterns. This method has so far been used only scarcely in ^{13}C NMR spectral analysis of complicated molecules, primarily because the determination of $^{13}C-^{1}H$ long-range coupling constant was difficult and the number of available long-range coupling constant values of aromatic compounds, especially nonheterocyclic molecules, is limited.[5]

One of the commonly encountered reactions which are fast on the NMR time scale is the intermolecular hydrogen exchange of labile protons between hydroxy groups. Dimethyl sulfoxide has been used as a solvent to inhibit proton exchange of alcohols in ^{1}H NMR.[6] A similar phenomenon can also be observed in ^{13}C NMR.[7] The measurement of the ^{13}C–OH coupling constants depends on the acidity or the exchange rate of the hydroxy proton. No ^{13}C–OH coupling can be detected, even in dimethyl sulfoxide solution, as evidenced by the fact that the identical spectra were obtained for phenol and deuteriophenol (OD) in deuteriochloroform and deuteriodimethyl sulfoxide solutions. The proton coupled spectra of phenol can be fully analyzed if Roberts' conclusion regarding the aromatic $^{13}C-^{1}H$ long-range coupling constants are accepted[5a] (Table I). It is interesting that $^{3}J_{CH}$ through an oxygen-substituted carbon is considerably reduced,[8] which has diagnostic value for analyzing very complicated spectra. Further studies of ortho-substituted phenols can thus be carried out (Table II).

Table I. $^{13}C-^{1}H$ Coupling Constants (hertz) of Phenol in $CDCl_3$[a]

	Carbon			
	1	2	3	4
Multiplicity	ttd	ddd	dd	dt
J (coupled proton)	8.9 (H_3) 2.5 (H_2) 1.3 (H_4)	158.5 (H_2) 7.8 (H_4) 4.2 (H_6)	160.1 (H_3) 8.4 (H_5)	161.6 (H_4) 7.3 (H_2)

[a] Maximum resolution, 0.24 Hz.

Simple chemical shift theory often leaves an ambiguity with respect to the differentiation of the C_4 and C_6 resonance signals of the above compounds.[9] Even the coupling patterns of the C_4 and C_6 signals in the proton-coupled spectrum of salicylaldehyde in deuteriodimethyl sulfoxide solution are identical. However, a clear distinction can be made in the spectrum in deuteriochloroform solution (Figure 1a). The high field portion of C_6 signal gives an extra splitting of which probably results from the coupling with the hydroxy proton, whose exchange rate is greatly reduced by the intramolecular hydrogen bonding.[10] This is confirmed by the disappearance of this extra splitting in the spectrum of deuteriosalicylaldehyde (OD) (Figure 1b). This hydrogen bond is still retained in deuterioacetone solution. This means that ^{13}C NMR can

Table II. ^{13}C Chemical Shifts (δ) and $^{13}C-^{1}H$ Coupling Constants of Phenols[a]

	Carbon						
	1	2	3	4	5	6	7
				Salicylaldehyde (1) in $CDCl_3$			
δ (multiplicity)	160.9 (m)	120.3 (m)	133.4 (ddd)	119.5 (dd)	136.5 (dd)	117.0 (dtt)	196.2 (dd)
J (coupled proton)			159.8 (H_5) 8.8 (H_3) 1.0 (H_4)	165.5 (H_4) 7.9 (H_2)	161.0 (H_3) 8.7 (H_5)	162.7 (H_2) 7.5 (H_4) 7.5 (OH) 1.6 (H_3) 1.6 (H_5)	177.2 (H_{CO}) 6.0 (H_5)
				Salicylic Acid (3) in Acetone-d_6			
δ (multiplicity)	162.2 (tdd)	112.4 (ddd)	130.5 (dddd)	119.1 (ddd)	135.9 (ddd)	117.3 (ddd)	171.9 (dt)
J (coupled proton)	9.2 (H_3) 9.2 (H_5) 3.3 (H_2) 1.6 (H_4)	8.2 (H_4) 5.1 (H_6) 1.4 (H_5)	162.0 (H_5) 5.6 (H_3) 2.7 (H_4) 0.9 (H_2)	163.6 (H_4) 8.1 (H_2) 1.0 (H_3 or H_5)	160.8 (H_6) 9.3 (H_5) 0.8 (H_2 or H_4)	162.5 (H_6) 7.6 (H_4) 1.2 (H_5)	3.5 (H_5) 1.0 (H_4) 1.0 (H_2)
				Methyl Salicylate (4) in $CDCl_3$			
δ (multiplicity)	161.0 (m)	111.6 (dt)	129.1 (ddd)	118.2 (ddd)	134.7 (dd)	116.6 (dt)	169.7 (m)
J (coupled proton)		8.3 (H_4) 4.4 (H_6) 4.4 (OH)	161.9 (H_5) 8.2 (H_3) 3.1 (H_4)	162.8 (H_4) 8.1 (H_2) 1.2 (H_3 or H_5)	160.7 (H_3) 9.3 (H_5)	162.4 (H_2) 7.7 (H_4)	

[a] Small coupling constants (<0.8 Hz) are not included. Maximum resolution, 0.24 Hz; δ (parts per million) downfield from TMS; m, unresolved multiplet.

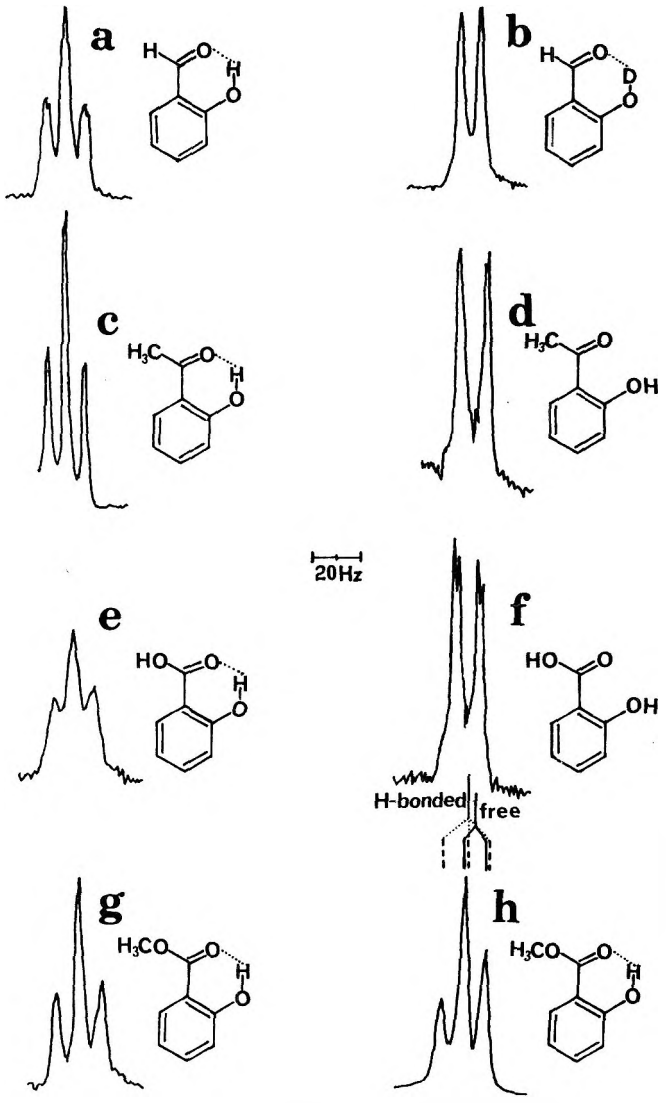
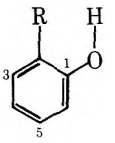


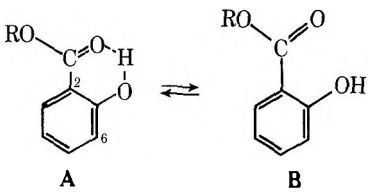
Figure 1. The high field portion of the C_6 signal of ortho-substituted phenols: (a) salicylaldehyde in $CDCl_3$; (b) deuteriosalicylaldehyde (OD) in $CDCl_3$; (c) o-hydroxyacetophenone in $CDCl_3$; (d) o-hydroxyacetophenone in Me_2SO-d_6; (e) salicylic acid in ethyl ether; (f) salicylic acid in acetone-d_6; (g) methyl salicylate in $CDCl_3$; (h) methyl salicylate in Me_2SO-d_6. The small splittings (<1 Hz) are due to two-bond coupling.

also provide us a direct method to measure the relative strength of intra- vs. intermolecular hydrogen bondings in different solvents. o-Hydroxyacetophenone (2) gave similar results (Figure 1c and 1d). The C_6 signal of salicylic acid (3)



1, R = CHO
2, R = CH_3CO
3, R = CO_2H
4, R = CO_2CH_3

in deuterioacetone solution appears as double doublet (Figure 1f) indicating the absence of intramolecular hydrogen bonding or rapid equilibration between the conformers **3A** and **3B**,



A B

which may be due to the catalytic function of the carboxyl proton in enhancing the equilibration rate.

Many investigators in the field of physical organic chemistry have been concerned about the poor correlations obtained by the Hammet σ-ρ approach[11] for rate or equilibrium data of ortho-substituted benzene derivatives. A mathematical separation of these interactions in a linear fashion is often difficult and unrewarding.

The studies of meta- and para-substituted phenols in dimethyl sulfoxide solution have demonstrated a linear correlation of the hydroxyl chemical shifts with Hammett σ^- constants.[12] Tribble and Traynham[13] thus attempted to give an unambiguous mathematical description of the electronic or proximity effect of ortho substituents by determining ortho-substituent constants (σ_o^-) from the chemical shift measurements of the strongly intermolecularly hydrogen-bonded phenolic proton in dimethyl sulfoxide solution. Two extreme deviations (o-NO_2, and o-$COCH_3$) were ascribed to intramolecular hydrogen bonding, but, from the proton coupled spectrum of acetophenone (2) in the "regular" deuteriodi-

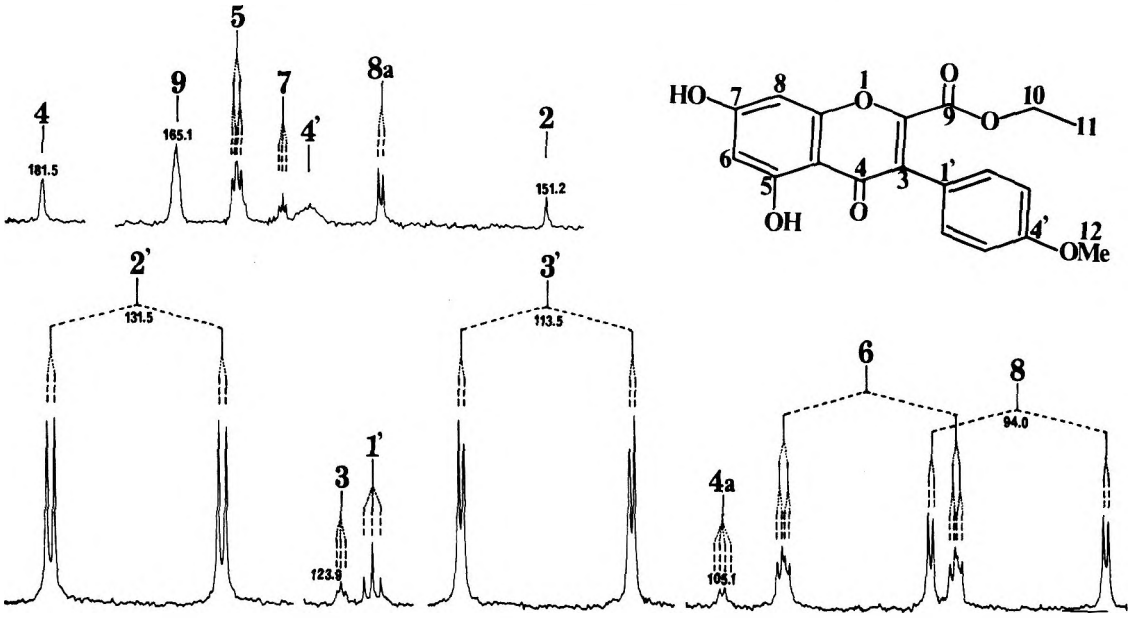
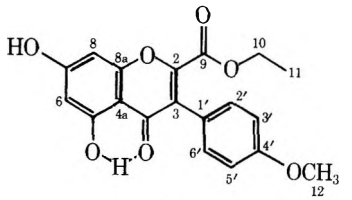


Figure 2. The proton coupled ^{13}C spectrum of aromatic carbon portion of 2-carbethoxy-5,7-dihydroxy-4′-methoxyisoflavone (5) in deuterioacetone solution.

methyl sulfoxide solution [50% (v/v)] (Figure 1d), the presence of a significant amount of the conformer (**2B**) is clearly indicated. They also stated that methyl salicylate (**4**) did not form an intramolecular hydrogen bond to any significant degree. In contrast, the ^{13}C NMR spectra of methyl salicylate in the same "regular" deuteriodimethyl sulfoxide solution [50% (v/v)] clearly reveals the existence of the intramolecularly hydrogen-bonded conformer (**4A**) (Figure 1g and 1h), which is in accord with Curtin's and Byrn's infrared study.[14] The ratio of these two representative conformers (**4A/4B**) is 1.77.[15] Their equilibration rate is enhanced by acid and depends on temperature. At 118 °C the C_1 signals of **4A** (160.9 ppm at 25°C) and **4B** (160.7 ppm at 25 °C) coalesce, and the ^{13}C–^1H three-bond coupling vanishes. In view of these discrepancies, it must be cautioned against the use of the ortho-substituent constants derived from the earlier ^1H NMR studies.[12] Among the results of the complete analysis of the ^{13}C–^1H long-range coupling constant it is worth noting that the syn ^{13}C–^1H coupling constant ($^3J_{C_2\text{-}OH}$ = 4.4 Hz) is considerably smaller than the anti coupling constant ($^3J_{C_6\text{-}OH}$ 8.3 Hz), analogous to the olefinic system.[5e] Therefore, ^{13}C–^1H long-range coupling constants can be useful in the conformational study of the hydroxy functional group.

The complete analysis of the ^{13}C spectrum of an isoflavone derivative (**5**) can further illustrate the potential usefullness



5

of ^{13}C–^1H long-range coupling constants (Figure 2).[16] Using the additivity principle of chemical shift theory, it is difficult to differentiate C_5, C_7, C_{8a}, and $C_{4'}$ and to distinguish the C_8 from C_6, and C_3 from $C_{1'}$ resonance signals. However, the detailed analysis of the long-range ^{13}C–^1H coupling constants allows one to completely resolve these ambiguities. In the proton-coupled spectrum in deuterioacetone solution, $C_{4'}$ shows as an unresolved multiplet at 160.2 ppm due to coupling with the methoxy protons, $H_{2'}$ and $H_{6'}$, and possibly with $H_{3'}$ and $H_{5'}$. C_{8a} has only one two-bond proton (H_8) and thus appears as a doublet at 157.5 ppm. A triplet at 161.1 ppm can be assigned to C_7, since only this carbon possesses two two-bond protons (H_6 and H_8). The C_5 signal is split into a double doublet owing to the coupling with H_6 and hydroxy proton which strongly indicates the intramolecular hydrogen bonding between this hydroxy group and the C_4 carbonyl group. This hydrogen bonding also results in the further splitting of C_6 signal ($^3J_{C_6\text{-}OH}$ = 7.0 Hz), which is shown as double doublet of doublets at 99.6 ppm while the C_8 signal appears as double doublet at 94.0 ppm. C_{4a} is shown as a quartet due to the long-range coupling with H_6, H_8, and C_5–OH protons. Here, the stereospecificity of the three-bond ^{13}C–^1H coupling is disclosed again [$^3J_{C_{4a}\text{-}OH}$ = 4.3 Hz (syn); $^3J_{C_6\text{-}OH}$ = 7.0 Hz (anti)]. $C_{1'}$ can be easily distinguished from C_3 by its normal three-bond coupling constant ($^3J_{C_{1'}\text{-}H_{3'(5')}}$ = 8.0 Hz), whereas the $^3J_{C_3\text{-}H_{2'(6')}}$ is reduced to 4.0 Hz. The carbons $C_{3'(5')}$ couples with $H_{5'(3')}$ through the oxygen-substituted carbon. The singlet at 151.2 ppm is assigned to C_2 simply because it is the only aromatic carbon without any two- or three-bond proton.

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(8) (a) From a large number of accumulation of high resolution spectra of aromatic compounds, this conclusion may be held for most electronegative substituents. Further results will be published soon. (b) First-order analysis was carried out. However the spectra of *o*-hydroxyacetophenone (**2**) appear non first order, and further detailed calculation will be necessary to unravel its precise long-range coupling constants.

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(16) Very recently Wehrli and Kinsbury also applied the long-range couplings in their partial spectral analysis of flavonoids: (a) F. W. Wehrli, *J. Chem. Soc., Chem. Commun.*, 663 (1974); (b) C. A. Kingsubury and J. H. Looker, *J. Org. Chem.*, **40**, 1120 (1975).

Ching-jer Chang

Department of Medicinal Chemistry and Pharmacognosy
School of Pharmacy and Pharmacal Sciences
Purdue University, West Lafayette, Indiana 47907

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Carbon Acids. 8. The Trimethylammonio Group as a Model for Assessing the Polar Effects of Electron-Withdrawing Groups

Summary: The relative size of polar and resonance contributions for CH_3CO, PhCO, $PhSO_2$, CN, and NO_2 groups in stabilizing a number of carbanions has been assessed from equilibrium acidity measurements by using the trimethylammonio group, Me_3N^+, as a model for the polar effect.

Sir: The trimethylammonio group, Me_3N^+, is unique in that it exerts a strong polar action and yet is incapable of acting as a π acceptor. As such, it has frequently been used as a model for judging the polar character of electron-withdrawing groups, G, and, from this, the extent to which G is capable of acting as a π acceptor when interacting with an acidic site across a benzene ring, as in p-$GC_6H_4NH_3^+$ or p-GC_6H_4OH.[1-3] We now wish to report results in which the effect of Me_3N^+ is used as a model to assess the resonance vs. polar character

Table I. Equilibrium Acidities in Dimethyl Sulfoxide Solution for Carbon Acids, GCH_2EWG[a]

G	pK (GCH_2CN)	pK (GCH_2SO_2Ph)	pK (GCH_2COPh)
H	31.3	29.0	24.6
Me	32.5[b]	31.0	24.4
Me_3C		31.2[c]	25.3[c]
Me_3N^+	20.6	19.4	14.6
CH_3CO		12.5	12.7
PhCO	10.2	11.4	13.1
$PhSO_2$	12.0	12.2	11.4
CN	11.1	12.0	10.2
NO_2		7.1	7.7

[a] The data for G = Me_3N^+ are from the present work; each acidity constant was determined from at least two three-point titrations with at least two indicators, and are reproducible to better than ±0.1 pK unit. Other pK's are from ref 4 or 17, or from unpublished work from this laboratory. [b] Estimated assuming an average of ΔpK for $MeCH(CN)_2$ vs. $HCH(CN)_2$ and $MeCH(Ph)CN$ vs. $HCH(Ph)CN$. [c] Determined with only one indicator.

of G when attached directly at the acidic site in a carbon acid, GCH_2EWG, where EWG is CN, $PhSO_2$, CH_3CO, PhCO, or NO_2.

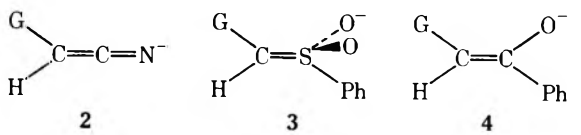
The positions of the equilibria described in eq 1, which can be determined indirectly by the competitive indicator method in dimethyl sulfoxide (Me_2SO) solution,[4] are governed for a given EWG, by the polar effect of G and by the ability of G to delocalize the charge in these highly basic anions.

$GCH_2EWG \rightleftarrows$

$$H^+ + G\text{—}\bar{C}H\text{—}EWG \leftrightarrow G\text{—}CH{=}E\bar{W}G \leftrightarrow \bar{G}{=}CH\text{—}EWG \quad (1)$$
$$\text{1a} \qquad\qquad \text{1b} \qquad\qquad \text{1c}$$

When G is H, Me, t-Bu, or Me_3N^+ resonance contributor **1c** is of little or no importance. The increase in acidity when G is Me_3N^+, compared with when G is H, Me, or t-Bu, can then be taken as a measure of the polar effect of Me_3N^+, since the polar effects of H, Me, and t-Bu are close to zero. The data in Table I show that this increase is large, ranging from ~9 to 12 pK units (equivalent to 13 to 16.5 kcal/mol) depending on the carbon acid system and model chosen. Choosing ΔpK between $MeCH_2EWG$ vs. $Me_3N^+CH_2EWG$ as a reasonable model of the polar effect of Me_3N^+, we can use σ_I for Me_3N^+ (0.82[5]) to obtain ρ_I from the Taft equation, $\Delta pK = \sigma_I\rho_I$. An estimate of the polar contribution for each group, G, can then be obtained from ρ_I and the σ_I constants for G (Table II).

We must emphasize at the outset that the results in Table II represent only a rough approximation of relative polar and resonance contributions of G. The Me group in $MeCH_2EWG$ is obviously a poor model, both sterically and electronically, for Me_3N^+.[11] Furthermore, the steric relationships of G to the negative charge center in the anions obviously change markedly in the three carbon acid systems (compare, e.g., **2**, **3**, and **4**). Nevertheless, despite the crudeness of the model, the differences observed are so large and so consistent for the various carbon systems that we believe significant conclusions can be drawn from the data in Table II.



2 **3** **4**

Note first that, although the ΔpK's for Me_3N^+ are large, the ΔpK's observed for the other groups are always larger. Since, by any account, the polar effect (σ_I) for Me_3N^+ is larger than

Table II. Estimate of Polar and Resonance Contributions to the Acidifying Effects of G in GCH_2CN, GCH_2SO_2Ph, and GCH_2COPh Carbon Acids

G	σ_I[a]	ΔpK_{calcd}[b]	ΔpK_{obsd}[c]	$\Delta\Delta pK$
GCH_2CN Carbon Acids; ρ_I = 14.5				
Me	−0.04[d]		(0.0)	
Me_3N^+	0.82[e]	(11.9)	11.9	
PhCO	0.30[f]	4.3	22.3	18.0
CN	0.56	8.1	21.4	13.3
$PhSO_2$	0.57[g]	8.3	20.5	12.2
GCH_2SO_2Ph Carbon Acids; ρ_I = 14.1				
Me	−0.04[d]		(0.0)	
Me_3N^+	0.82[e]	(11.6)	11.6	
CH_3CO	0.28	4.0	18.5	14.5
PhCO	0.30[f]	4.2	19.6	15.4
CN	0.56	7.9	19.0	11.1
$PhSO_2$	0.57[g]	8.1	18.8	10.7
NO_2	0.65	9.2	23.9	13.7
GCH_2COPh Carbon Acids; ρ_I = 11.9				
Me	−0.04[d]		(0.0)	
Me_3N^+	0.82[e]	(9.8)	9.8	
CH_3CO	0.28	3.3	11.7	8.4
PhCO	0.30[f]	3.6	11.3	7.7
CN	0.56	6.7	14.2	7.5
$PhSO_2$	0.57[g]	6.8	13.0	6.2
NO_2	0.65	7.8	16.7	8.9

[a] From ref 10 unless otherwise noted. [b] From $\Delta pK = \sigma_I\rho_I$. [c] From the data in Table I relative to $MeCH_2EWG$.[11] [d] Taken as zero in the calculation of ρ_I. [e] See ref 5. [f] Estimate (assuming a slightly larger value than for CH_3CO). [g] See ref 8.

for any uncharged group, it follows that all of the other groups being considered (CH_3CO, PhCO, $PhSO_2$, CN, and NO_2) must be exerting stabilizing effects on the carbanions that are much larger than those expected from their polar contributions. The $\Delta\Delta pK$'s in Table II provide a rough estimate of the sizes of these (resonance) effects. They range from 6.2 to 18.0 pK units, equivalent to 8.5 to 25 kcal/mol, depending on the group and the carbon acid system into which it is substituted. In the GCH_2CN and GCH_2SO_2Ph systems the resonance effects for all groups are much larger than their (calculated) polar effects. *This is contrary to the effect of* p-*G in benzene systems, where the polar contribution is usually dominant.*[3,10,12]

For a given group, G, $\Delta\Delta pK$ always decreases as the acidity of the parent model acid, $MeCH_2EWG$, increases.[14] The size of $\Delta\Delta pK$ is always larger for the carbonyl functions, CH_3CO and PhCO, than for the cyano or phenylsulfonyl functions, the latter two being nearly equal. (This is consistent with expectations from σ_R^- values.[10]) The large size of $\Delta\Delta pK$ for $PhSO_2$ (7.0 to 13.2 pK units) supports the conclusion that this function is capable of a strong conjugative interaction with an α carbanion,[16] comparable in size with that of the cyano function, but somewhat smaller than that of carbonyl or nitro functions.

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(11) The Me_3C group is a better model sterically than Me, but, since the differences in acidities between Me_3CCH_2EWG and $MeCH_2EWG$ are small, compared to $Me_3N^+CH_2EWG$, it makes but little difference which model is used.
(12) Polar contributions are clearly dominant according to the Swain–Lupton analysis.[3] Judging from the relative size of σ_I and σ_R^-, polar contributions are dominant according to the Ehrenson, Brownlee, and Taft dual parameter analysis, except for CH_3CO type substituents.[13] These analyses are based on oxygen and nitrogen acid systems. For carbon acid systems, *p*-$G_6H_4CH_2EWG$ our results to date suggest that polar and resonance contributions are more nearly equal.
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F. G. Bordwell,* Michael Van Der Puy, Noel R. Vanier
Department of Chemistry, Northwestern University
Evanston, Illinois 60201
Received March 19, 1976

Carbon Acids. 9. The Effects of Divalent Sulfur and Divalent Oxygen on Carbanion Stabilities

Summary: Using the trimethylammonio group, Me_3N^+, as a model to calculate the polar effect, the carbanion stabilizing effects of MeO and PhO groups have been found to be smaller than calculated, and the carbanion stabilizing effects of MeS and PhS groups have been found to be much larger than calculated.

Sir: There is long-standing and abundant evidence in the literature to indicate that divalent sulfur causes an adjacent C–H bond to be much more susceptible to cleavage by base than does divalent oxygen.[1] The greater kinetic acidity produced by α-RS (or α-PhS) than α-RO (or α-PhO) groups has been assumed by most experimentalists to be associated with a greater ability of divalent sulfur to stabilize an incipient carbanion in the transition state of the deprotonation reactions by a conjugative effect involving 3d orbitals.[1] On the other hand, theoreticians have generally been skeptical of the need to invoke such conjugative interactions.[2] For example, recent ab initio calculations have failed to reveal any role for 3d orbital conjugation in stabilizing the $HSCH_2^-$ anion, and the conclusion has been drawn that sulfur stabilizes carbanions by polarization, rather than by d-orbital conjugation.[3]

In the previous paper in this series[4] we used the difference in acidities (ΔpK) of $Me_3N^+CH_2EWG$ and $MeCH_2EWG$ (EWG = CN, $PhSO_2$, or PhCO) as a measure of the sensitivities of these carbon acids to polar effects, $\Delta pK = \sigma_I\rho_I$. The ρ_I values were then used in conjunction with σ_I to estimate the polar effect anticipated for a group, G, in the GCH_2CN, GCH_2SO_2Ph, and GCH_2COPh carbon acid systems. When G is a π acceptor it should stabilize the $GCHEWG^-$ anion by conjugation, as well as by a polar effect, and the increase in acidity observed should be larger than that calculated from the $\sigma_I\rho_I$ relationship. This was found to be true when G is a strong π-acceptor group (CH_3CO, PhCO, NO_2, $PhSO_2$, CN), the $\Delta\Delta pK$'s ranging from 6.2 to 18.0 pK units.[4] If RS or PhS groups have π-acceptor capacity, we would then expect to find that the acidities are enhanced to an extent greater than expected on the basis of their polar effects; no enhancement is expected, of course, for RO and PhO groups. The results are summarized in Table I for four carbon acid systems.

Table I. Comparison of the Acidifying Effects of MeO, PhO, MeS, and PhO Groups with the ir Polar Acidifying Effects

G	σ_I[a]	ΔpK_{calcd}[b]	ΔpK_{obsd}[c]	$\Delta\Delta pK$[d]
A. GCH_2CN Carbon Acids; $\rho_I = 14.5$				
Me	−0.04[e]	(0.0)	(0.0)	
Me_3N^+	0.82[f]	(11.9)	11.9	
PhO	0.38	5.2	4.4	−0.8
PhS	0.30[g]	4.4	11.7	7.3
B. GCH_2SO_2Ph Carbon Acids; $\rho_I = 14.1$				
Me	−0.04[e]	(0.00)	(0.0)	
Me_3N^+	0.82[f]	(11.6)	11.6	
MeO	0.27	3.8	0.3	−3.5
PhO	0.38	5.3	3.1	−2.2
MeS	0.23	3.2	7.6	4.4
PhS	0.30[g]	4.2	10.5	6.3
C. GCH_2COPh Carbon Acids; $\rho_I = 11.9$				
Me	−0.04[e]	(0.0)	(0.0)	
Me_3N^+	0.82[f]	(9.8)	9.8	
MeO	0.27	3.2	1.5	−1.7
PhO	0.38	4.5	3.3	−1.2
PhS	0.30[g]	3.6	7.3	3.7
PhSe	0.24[h]	2.9	5.8	2.9
D. 9-G-Fluorene Carbon Acids; $\rho_I = 8.1$				
Me	−0.04[e]		(0.0)	
Me_3C	−0.07[e]	(0.0)		
Me_3N^+	0.82[f]	(6.55)	6.55[i]	
MeO	0.27	2.2	0.2	−2.0
PhO	0.38	3.1	2.4	−0.7
MeS	0.23	1.9	4.3	2.4
PhS	0.30[g]	2.4	6.9	4.5

[a] From ref 9 unless otherwise noted. [b] From $\Delta pK = \sigma_I\rho_I$. [c] Relative to the p$K$ of $MeCH_2CN$ (32.5, series A), or $MeCH_2SO_2Ph$ (31.0, series B), or $MeCH_2COPh$ (24.4, series C), or 9-methylfluorene (22.3, series D). [d] $\Delta\Delta pK = \Delta pK_{obsd} - \Delta pK_{calcd}$. [e] Taken as (0.0). [f] An average value; see footnote 5 of ref 4. [g] See ref 10. [h] Calculated from 0.45 $\sigma^*_{CH_2SePh}$ using the data of L. D. Pettit, A. Royston, C. Sherrington, and R. J. Whewell, *J. Chem. Soc.* B, 588 (1968). [i] Relative to 9-*tert*-butylfluorene (pK = 24.55).

For reasons given earlier,[4] we do not expect the Me group in $MeCH_2EWG$ to be a good model sterically or electronically for the Me_3N^+ group in $Me_3N^+CH_2EWG$. In addition, the steric relationships between G and the site of electron charge density changes for the various $GCHEWG^-$ anions.[4] Steric effects for 9-substituted fluorenes are more severe than in the GCH_2EWG carbon acids. In fluorene, substitution of Me_3C for H at the 9 position causes a 1.7 pK unit decrease in acidity, whereas substitution of Me for H causes a 0.5 pK unit *increase* in acidity. In the fluorene system 9-*tert*-butylfluorene has been used as a model for 9-trimethylammoniofluorene, but 9-methylfluorene has been used as a model to calculate ΔpK's for 9-MeO-, 9-PhO-, 9-MeS-, and 9-PhS-fluorenes. Although the difficulties in choosing proper models are such as to make the calculations of polar effects of an approximate nature, the

results obtained for the various carbon acid systems are consistent and we believe that the $\Delta\Delta pK$'s are significant.

Note first that the $\Delta\Delta pK$'s for MeO and PhO groups are negative in every instance, i.e., the observed ΔpK's are *smaller* than those expected on the basis of the polar effect. This is a pattern that has been observed previously for the effect of α-MeO substituents on the base-catalyzed exchange rates for deprotonation of acetates, GCH_2CO_2Me, and their cyclic analogs.[5] It has been suggested that, when G = MeO, the incipient carbanion produced in the transition state for these deprotonations is destabilized by an electronegativity effect and by lone pair–lone pair interactions.[5] Such destabilizing effects by MeO or PhO in the carbanions, $MeOCHEWG^-$ and $PhOCHEWG^-$ would account for the negative $\Delta\Delta pK$ values in Table I.

In sharp contrast to the negative $\Delta\Delta pK$'s observed for PhO, the $\Delta\Delta pK$'s for PhS are all positive and large, ranging from 3.7 to 7.3 pK units. This suggests stabilization of the anions over and above that expected from a polar effect of the order of 6 to 10 kcal/mol. These effects are similar to those observed with strong π-acceptor groups,[4] although they are somewhat smaller in magnitude.

The strikingly large acidifying effect of the PhS group can be brought out further by some direct comparisons of the pK data. Despite the much smaller polar effect of PhS ($\sigma_I = 0.30$) than Me_3N^+ ($\sigma_I = 0.82$), $PhSCH_2SO_2Ph$ is only 0.9 pK unit less acidic than $Me_3N^+CH_2SO_2Ph$, $PhSCH_2CN$ is only 0.2 pK unit less acidic than $Me_3N^+CH_2CN$, and 9-PhS-fluorene (pK = 15.4) is 2.4 pK units *more* acidic than 9-Me_3N^+-fluorene (pK = 17.8).

It is difficult to decide whether these large effects are caused *solely by the high degree of polarizability of sulfur, as the ab initio* calculations suggest,[3] or whether a conjugative effect is also operative. Several results from our pK data lead us to believe that more than polarizability is involved. Note, for example, that $\Delta\Delta pK$ is greater for $PhSCH_2COPh$ (3.7) than for $PhSeCH_2COPh$ (2.9), despite the greater polarizability of selenium. In addition, Hammett correlations for equilibrium acidities in Me_2SO in both the meta- and para-substituted phenylacetonitrile system[6] and the 3-substituted fluorene system,[7] require σ_p^- for PhS, rather than σ_p, despite the fact that resonance effects are greatly attenuated when operating across a benzene ring.[4] Finally, there is strong evidence that the F_3CSO_2 and $PhSO_2$ groups enter into conjugation based *on their strong acidifying effect on methane and the diminution* of this effect when the substituent is placed on a cyclopropane ring.[8] Since tetravalent sulfur can exert strong conjugative effects, it seems likely that divalent sulfur can also enter into electron acceptor conjugation with α carbanions.

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F. G. Bordwell,* Michael Van Der Puy, Noel R. Vanier
Department of Chemistry, Northwestern University
Evanston, Illinois 60201
Received March 19, 1976

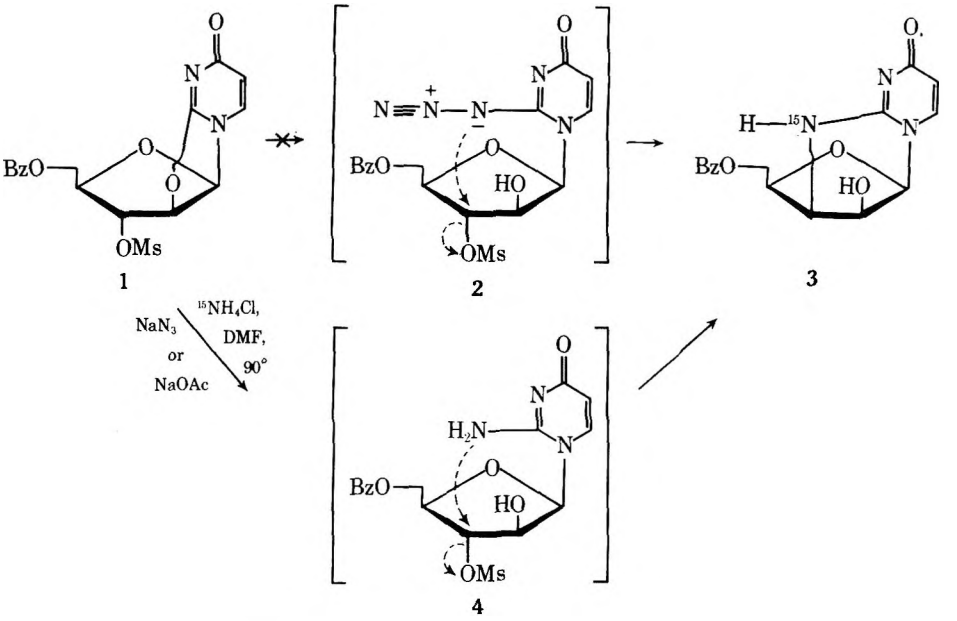
Nucleic Acid Related Compounds. 19. Concerning the Mechanism of Formation of "2,3'-Imino-1-(β-D-lyxofuranosyl)uracil" [2-Amino-1-(3-deoxy-β-D-lyxofuranosyl)-4-pyrimidinone-N^2→3'-anhydronucleoside] from O^2→2' Cyclonucleosides and "Ammonium Azide"[1]

Summary: Postulated attack of azide anion (from "ammonium azide") at C^2 of the pyrimidine ring of O^2→2' cyclonucleoside **1** followed by intramolecular cyclization with accompanying loss of nitrogen gas to give N^2→3' cyclonucleoside **3** does not occur, as was demonstrated by incorporation of ^{15}N from labeled ammonium chloride and verified by analogous formation of **3** using "ammonium acetate".

Sir: In a very recent issue of this journal, the conversion of O^2→2'-anhydro-1-(5-*O*-benzoyl-3-*O*-methanesulfonyl-β-D-arabinofuranosyl)uracil (**1**) and related O^2→2' cyclonucleosides to the corresponding N^2→3'-anhydro-2-amino-1-(5-*O*-benzoyl-3-deoxy-β-D-lyxofuranosyl)-4-pyrimidinone (**3**) and related derivatives using "ammonium azide" in hot *N,N-dimethylformamide* (DMF) was described.[2] This transformation was postulated to proceed via azide attack at C^2 of the pyrimidine ring followed by an unusual intramolecular attack by the geminal electrons of N^1 of the azide moiety (intermediate **2**) to give **3** by an unexplained (necessarily reductive) process. Treatment of 5'-*O*-trityl-O^2→2'-anhydro-1-(β-D-arabinofuranosyl)uracil with "ammonium azide" in DMF at 110° was reported[2] to give 59% 1-(5-*O*-trityl-2-azido-2-deoxy-β-D-ribofuranosyl)uracil, plus 33% starting material, which is in agreement with previous studies of Moffatt and coworkers[3] involving SN2-type displacement of O^2 from $C^{2'}$ of an O^2→2' anhydronucleoside using lithium azide. An "unprecedented" "introduction of an azide group into pyrimidine bases through O^2 anhydronucleosides"[2] was proposed to explain the formation of **3**. A 'striking "through bond" electronegative influence to $C^{2'}$ was attributed[2] to the leaving group (mesylate) at $C^{3'}$ to rationalize azide attack at $C^{2'}$ in the 5'-*O*-trityl-3'-hydroxy compound (i.e., absence of the 3'-*O*-mesyl function).

Fox and coworkers[4] have reported that treatment of 3'-*O*-mesyl-O^2→5'-anhydrothymidine with ammonia at room temperature in a sealed vessel gave the N^2→3'-anhydro-2',3'-dideoxy compound (corresponding to **3**). Attack of ammonia at C^2 of the pyrimidine ring with displacement of alkoxide ($OH_2C^{5'}$ or OCH_3, from reaction with $MeOH/Et_3N$) was postulated with subsequent intramolecular displacement of mesylate by the exocyclic amino function of the isocytosine system to give the N^2→3' cyclonucleoside.[4]

In the present reaction, ammonium azide was assumed to be generated in situ from a sixfold molar excess of ammonium chloride and sodium azide.[2] This more soluble azide salt was the presumed nucleophile. However, the following acid–base equilibrium (eq 1) would be expected to provide a finite [pK_a



$$\overset{+}{N}H_4\overset{-}{Cl} + \overset{+}{Na}\overset{-}{N_3} \rightleftharpoons NH_3 + HN_3 + \overset{+}{Na}\overset{-}{Cl} \qquad (1)$$

$(NH_4Cl) = 9.25$, pK_a $(HN_3) = 4.72]$[5] steady-state concentration of ammonia, and Fox's results[4] would suggest that reaction of ammonia with cyclonucleoside **1** might be very rapid in DMF at 90 °C.

Treatment of **1**[6] with 99 atom % ^{15}N-ammonium chloride[7] and ^{14}N-sodium azide in DMF at 90 °C for 12 h and processing as described[2] gave 71% (65% recrystallized) **3**: mp 258–260 °C (after the first crystallization), mp 285–286 °C (after recrystallization); uv (0.1 N HCl) max 232 nm (ϵ 17 000), sh 264 (6700), min 216 (12 000); uv (MeOH) max 217 nm (ϵ 32 600), sh 227, 262 (29 700, 4400) [lit.[2] mp 250–252 °C; uv (MeOH) max 217 nm (ϵ 33 300), sh 261 (4000); yield 70%]. The mass spectrum of this product had *m/e* 330.0974, calcd for M^+ ($C_{16}H_{15}{}^{14}N_2{}^{15}NO_5$) 330.0982. Comparison of mass spectra (AEI MS-50 with computer averaging of nine scans under identical conditions) of this product and a sample prepared using $^{14}NH_4Cl$ indicated complete incorporation of ^{15}N. Therefore, displacement of O^2 at the pyrimidine terminus of **1** by ammonia to give intermediate **4** followed by intramolecular cyclization to **3** is compatible with the labeling experiment. If this interpretation is correct, reaction of **1** with ammonium chloride and the salt of an acid of comparable strength with that of hydrazoic acid would be expected to proceed analogously. Acetic acid ($pK_a = 4.76$)[5] and hydrazoic acid ($pK_a \sim 4.72$)[5] are almost identical in acid strength. Treatment of **1** with an eightfold molar excess of ammonium chloride and sodium acetate in DMF at 90 °C under identical conditions with those above resulted in formation of **3** in 82% (72% recrystallized) yield. Thus, there is no evidence for formation of **2** or the implausible mechanism noted.[2]

Doerr and Fox[8] have observed that 2-amino-1-(β-D-arabinofuranosyl)-4-pyrimidinone (1-β-D-arabinofuranosylisocytosine) is very easily (even during warming for recrystallization) converted to the $O^2 \rightarrow 2'$-anhydro uracil product by attack of the "up" $O^{2'}$ at C^2 with evolution of ammonia. Therefore, ammonia displacement of oxygen at the pyrimidine terminus of the 3′-hydroxy-$O^2 \rightarrow 2'$-anhydro compound[2] (analogous to intermediate **4**) would be unproductive since reversal to the $O^2 \rightarrow 2'$ cyclonucleoside would be expected to proceed readily in DMF at 110 °C.[8] In contrast, attack by azide at $C^{2'}$ would lead to the observed[2] 2′-azido-2′-deoxy uracil nucleoside, presumably irreversibly. Thus, azide attack at $C^{2'}$ of cyclonucleosides is the normal course[3] and does not result from absence of a "through bond" electronegative effect[2] in the case of the 3′-hydroxy compound. All chemistry involved in these reactions is in harmony with precedents[3,4,8] in the literature.

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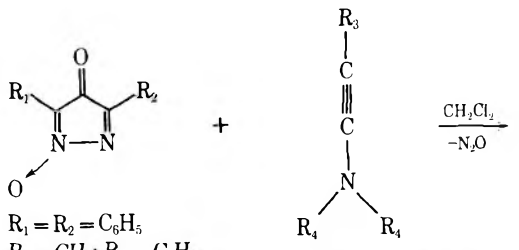
Morris J. Robins,* Tadashi Kanai[9]
Department of Chemistry, The University of Alberta
Edmonton, Alberta, Canada T6G 2G2
Received February 17, 1976

Synthesis of 3-Dialkylaminocyclopentadienones[1]

Summary: The title compounds are prepared by condensation of 3,4-diazacyclopentadienone 3-oxides with ynamines. The regiospecificity of the reaction was proven by hydrolysis of the amines to cyclopentene-3,5-diones.

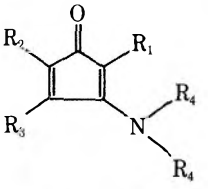
Sir: The cycloaddition chemistry of 3,4-diazacyclopentadienone oxides[2] and related compounds[3,4] with acetylenes has previously been reported and involved deep-seated rearrangements which could be rationalized from a first-formed 1,3-dipolar cycloadduct. In contrast with these results we have now found that ynamines (**2**) condense with 3,4-diazacyclopentadienone 3-oxides (**1**) in a Diels–Alder sense to produce 3-dialkylaminocyclopentadienones (**3**) in good yields (60–70%). These are the first representatives of this group of compounds to be reported.

In a typical preparation addition of 1.1 equiv of ynamine **2** to a stirred solution of **1** (1 equiv) in CH_2Cl_2 led to an exo-



1a, $R_1 = R_2 = C_6H_5$
b, $R_1 = CH_3$; $R_2 = C_6H_5$

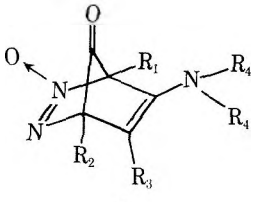
2a, $R_3 = CH_3$; $R_4 = C_2H_5$
b, $R_3 = C_6H_5$; $R_4 = CH_3$



3a, $R_1 = R_2 = C_6H_5$; $R_3 = CH_3$; $R_4 = C_2H_5$ (mp 96-97 °C)
b, $R_1 = R_2 = R_3 = C_6H_5$; $R_4 = CH_3$ (mp 152-153 °C)
c, $R_1 = R_4 = CH_3$; $R_2 = R_3 = C_6H_6$ (mp 140-142 °C)

thermic reaction and gas (N_2O) was immediately evolved. Evaporation of the solvent and chromatography of the resulting residue on a neutral alumina column with $CHCl_3$ as the eluent yielded the cyclopentadienones **3** as purple[5] bands which were further purified by recrystallization from hexane.

This reaction appears to be a Diels–Alder reaction analogous to that of ordinary cyclopentadienones,[6] followed by the loss of nitrous oxide rather than carbon monoxide. However, the formation of the cycloadduct may not be concerted but rather a two-step process involving a nucleophilic attack of the ynamine on the heterocycle **1**, followed by collapse to the Diels–Alder adduct. Two possible regioisomers (**4** and **5**) could result. However, the condensation of the unsymmetrical 3,4-diazacyclopentadienone (**1b**) with ynamine **2b** yielded



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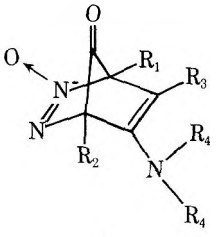

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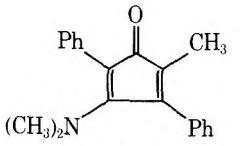
cyclopentadienone **3c** with no detectable amount of **6** (^1H NMR analysis) and thus established **4** as the intermediate. The structure of **3c** was established by hydrolysis in refluxing 5% $HClO_4$ to yield **7c**,[7] whose ^1H NMR spectrum unambiguously confirmed the structural assignment [δ_{CH_3} 1.37 (d, J = 7.5 Hz)].



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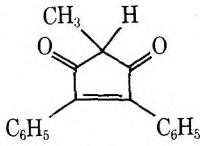

7c

This cycloaddition reaction is remarkably different from the earlier cycloadditions in this series,[2a] which presumably involve 1,3 cycloadditions across the nitrone group. The possibility of a common intermediate which partitions between a 1,3 cycloadduct and a 1,4 cycloadduct might explain this periselectivity. However, the regioisomer characterized from the cycloaddition of simple nitrones with ynamines[8] suggests that the partitioning intermediate would yield a 1,4 cycloadduct of structure **5**. Therefore, it is a reasonable assumption that the reaction involves a nucleophilic attack of the ynamine on the imine carbon[9] which then collapses to yield **4**.

Supplementary Material Available. Spectral data for compounds **3** and **7** (2 pp). Ordering information is given on any current masthead page.

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Jeremiah P. Freeman,* Raymond C. Grabiak
Department of Chemistry, University of Notre Dame
Notre Dame, Indiana 46556

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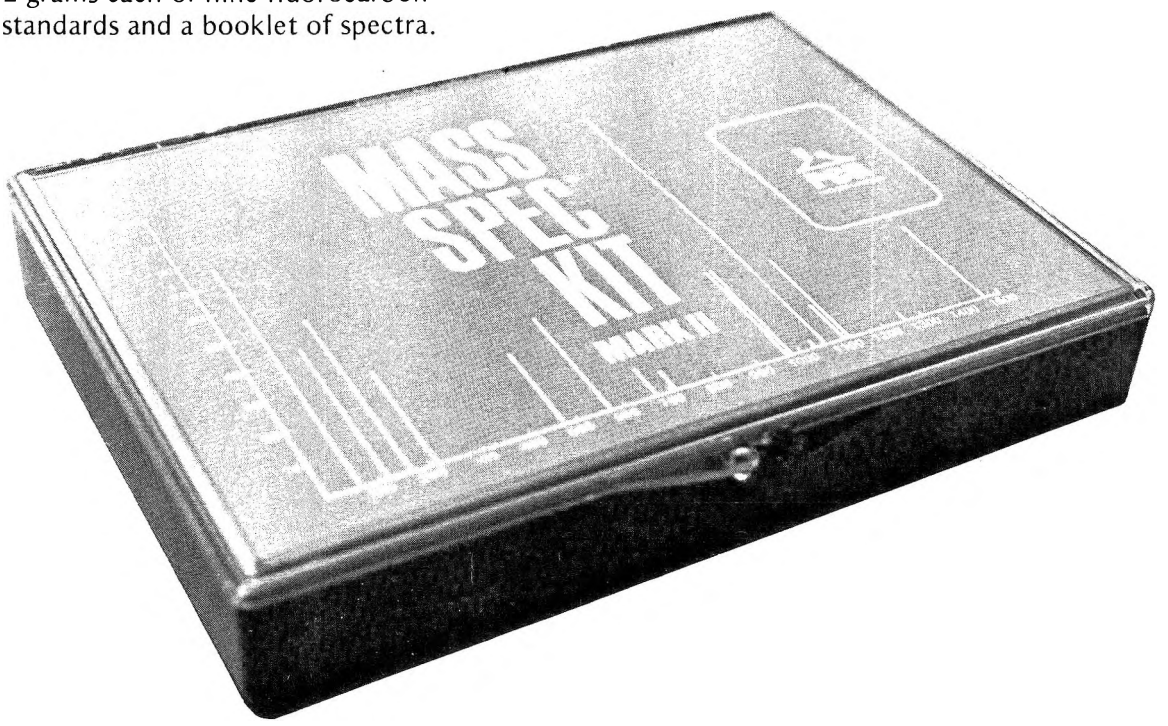

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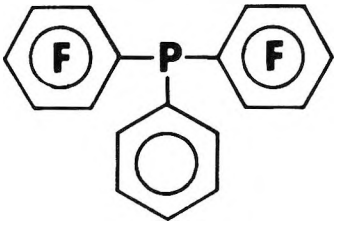

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