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THE JOURNAL OF Organic Chemistry®

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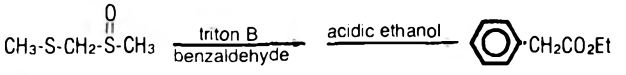
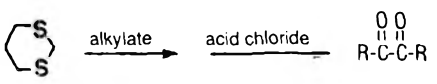
SULFUR ACTIVATED METHYLENES

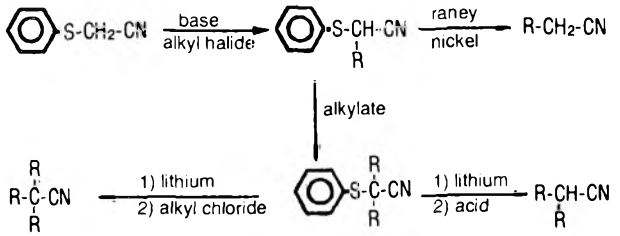
The utility of activated methylenes in organic synthesis is well known. Intermediates such as diethyl malonate and ethyl acetoacetate have innumerable uses. When we first advertised **Sulfonyl** Activated Methylenes we called them "Unexplored Territory." Things have changed since then. Now these, as well as other types of sulfur activated methylenes, have found a variety of applications in a wide range of organic syntheses.

FAMSO and m-Dithiane: These two bis(sulfur) activated methylenes are readily alkylated or dialkylated then hydrolyzed to yield aldehydes or ketones [1,2,3,4]. s-Trithiane may also be used to prepare aldehydes[5]. In addition these compounds may be used to produce phenylacetic acids[6], phenylacetic esters[7], amino acids[8] 1,2-diketones, 1,3-ketoaldehydes, 2-ketoacids, 2-hydroxy-1,3-diketones, 1,4-diketones, hydrocarbons, hydroxymethylketones, hydroxyethylketones, aminomethylketones, 2-ketoaldehydes, acylsilanes, and many others[9-14].

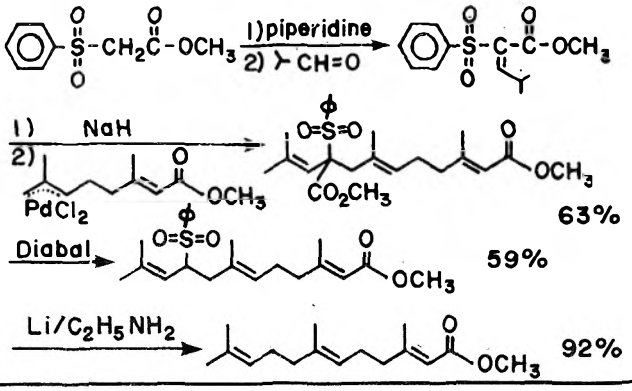




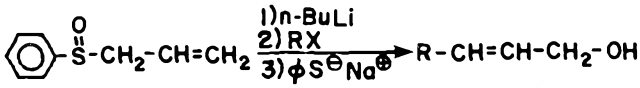
Sulfides: Sulfides bearing activating groups such as cyano, carbonyl or carbomethoxy are readily mono, di, or tri alkylated in high yield[15].



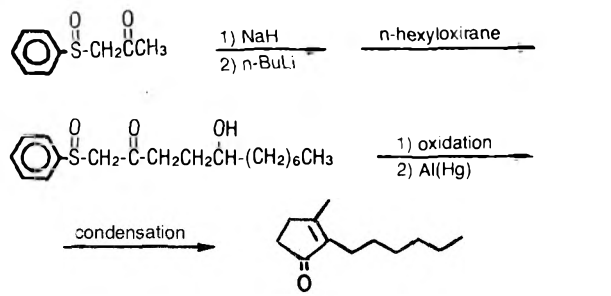
Isoprenylating Agents: Trost has recently introduced a new isoprenylating agent which functions with high stereospecificity and in high yield.[16] Stereospecificity is poor if the usual malonate esters are used in place of the sulfone[17].



Allyl Alcohol Reagent: Complex allylic alcohols are readily prepared from allyl aryl sulfoxides *via* alkylation followed by a sigmatropic shift and cleavage.[18]



Phenylsulfinylacetone: Grieco has recently reported a facile jasmone synthesis from this reagent [19]. Alkylation of sulfinyl and sulfonyl acetone dianions should prove to be a powerful tool in the synthesis of complex organic molecules.



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partial listing

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1966	**m-Dithiane:** acyl anion equivalent for carbonyl synthesis	12.85/25g	39.25/100g
1478	**2,2'-Ethylene bis (m-dithiane):** acyl anion equivalent for 1,4-dicarbonyl synthesis	19.75/25g	
2640	**Methyl isobutylidinylphenylsulfonylacetate:** isophrenylating agent	22.50/25g	
1238	**Allyl phenyl sulfoxide:** reagent for the synthesis of allyl alcohols	19.85/25g	61.15/100g
1339	**Phenyl sulfinylacetone:** jasmone intermediate	18.50/10g	
1713	**s-Trithiane:** acyl anion equivalent for aldehyde synthesis	12.00/50g	
2414	**Ethyl methylsulfonylacetate**	17.40/25g	53.60/100g
2411	**Methylsulfonylacetone**	17.50/25g	53.60/100g
1024	**Methylsulfonylacetonitrile**	15.75/25g	48.50/100g
1090	**Methylsulfonylacetophenone**	12.70/25g	39.10/100g
1132	**Methylsulfonylacetamide**	16.25/25g	49.95/100g
1490	**Ethyl methylthioacetate**	13.95/25g	42.90/100g
1491	**Methylthioacetamide**	13.95/25g	42.95/100g
1855	**Methylthioacetonitrile**	12.50/25g	38.50/100g
1313	**Methyl phenylthioacetate**	12.90/25g	34.75/100g
1315	**Methyl 2-phenylthiopropionate**	17.95/25g	
1273	**Phenylthioacetamide**	12.50/25g	38.50/100g
1987	**Phenylthioacetic acid**		12.50/100g
1334	**Phenylthioacetone**	12.50/25g	38.50/100g
1022	**Phenylthioacetonitrile**	11.70/25g	35.95/100g
1337	**Phenylthioacetophenone**	15.00/25g	46.30/100g
1236	**Allyl phenyl sulfide**	12.50/25g	38.50/100g
1253	**Methallyl phenyl sulfide**	12.50/25g	38.50/100g
1256	**Phenyl propargyl sulfide**	17.50/25g	
1095	**Ethyl phenylsulfonylacetate**	14.75/25g	45.50/100g
1318	**Methyl phenylsulfonylacetate**	13.80/25g	42.50/100g
1237	**Allyl phenyl sulfone**	13.50/25g	42.85/100g
1131	**Phenylsulfonylacetamide**	10.85/25g	33.50/100g
1093	**Phenylsulfonylacetone**	12.95/25g	39.95/100g
1023	**Phenylsulfonylacetonitrile**	11.75/25g	36.20/100g
1091	**Phenylsulfonylacetophenone**	15.50/25g	47.75/100g
1097	**Phenylsulfonylpinacolne**	11.75/10g	

For a more complete review of these and many other useful and unique reactions of sulfur activated methylenes, write for our free brochure entitled "Making It With Sulfur". For a complete listing of the more than 1000 compounds we offer, write for our catalog "The Philosophers' Stone".

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AUTHOR INDEX

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VOLUME 41, NUMBER 21

OCTOBER 15, 1976

Rates and Equilibria in Hydration and Bisulfite Addition by 1,3-Dimethoxyacetone[1]

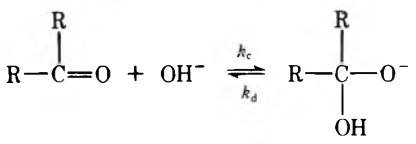
Jack Hine,* Lawrence R. Green, Paul C. Meng, Jr., and V. Thiagarajan

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

Received April 15, 1976

Equilibrium constants for the hydration of 1,3-dimethoxyacetone have been determined over the range 1.4–59.7 °C. The kinetics of hydration at 25 °C have been studied in cacodylic acid buffers around pH 6 and in triethylamine buffers around pH 11. The pK_a of the hydrate was found to be 13.17 at 25 °C. A study of equilibrium in bisulfite addition over the pH range 2.5–12.3 gave a pK_a of 9.89 for the hydroxylic hydrogen atom in $(MeOCH_2)_2C(OH)SO_3^-$ and an equilibrium constant of 880 M^{-1} for the formation of this anion from the ketone and bisulfite ion at 25 °C. The kinetics of the decomposition of the bisulfite addition compound at this temperature over the pH range 4.5–8.5 showed that the reaction involves largely rate-controlling decomposition of the dianion $(MeOCH_2)_2C(O^-)SO_3^-$, but leaves open the possibility of significant amounts of general catalysis of decomposition of the monoanion by the basic components of the buffers used. A method of determining the equilibrium constant for the hydration of the ketone was developed on the basis of the fact that bisulfite addition is much faster than hydration near pH 6. Stopped-flow measurements made when bisulfite addition was almost at equilibrium but very little hydration and dehydration had taken place gave equilibrium constants for hydration that confirmed the value obtained by injecting ketone into water and comparing initial and equilibrium absorbances. Rate constants for coodination of hydroxide ions and sulfite ions with the carbonyl carbon atom of 1,3-dimethoxyacetone were found to be smaller than analogous rate constants for reactions with aldehydes in cases where the reactions with the aldehydes had about the same equilibrium constants as the reactions with the ketone. This is attributed to steric hindrance being greater in the transition state than in the product of the reactions of these nucleophiles with aldehydes and ketones.

An earlier paper in this series dealt with correlations between rate constants and equilibrium constants for one-step Lewis acid–base reactions in which the electrophilic atom was carbon.[2] A plot of log k_c vs. log K_c for addition of hydroxide ions to acetone and seven aldehydes (eq 1) gave a reasonable approach to linearity. However, the compounds for which data were available were such that the effective size of the R's in eq 1 tended to decrease with increasing K. Therefore it seemed



(1)

possible that the slope of the line was partly a result of systematic changes in steric effects. It was therefore of interest to obtain data on a ketone for which K_c is as large as it is for some of the aldehydes. Data on reactions involving nucleophilic reagents other than hydroxide ion were also of interest. For these reasons we have studied the kinetics of the hydration of and the addition of sodium bisulfite to 1,3-dimethoxyacetone. Use of 1,3-dimethoxyacetone as a model for the physiologically important compound 1,3-dihydroxyacetone also makes these studies of interest. The hydroxylic hydrogen atoms of 1,3-dihydroxyacetone so increase the number of ways that the compound can react that 1,3-dimethoxyacetone can provide some useful simplification of the possible reaction schemes.

Results

Equilibrium in Hydration. The hydration reaction was first studied by a procedure[3,4] in which the ketone was dissolved in an aqueous solution and the absorbance near its uv absorption maximum monitored. In order to follow this rather rapid reaction over as wide a range of reaction as possible, the ketone was injected into an aqueous solution that was being stirred while in a spectrophotometer.[5] Points taken after about 5 s followed a first-order rate equation rather closely, but points taken earlier had too large an absorbance to fit the rate constant obtained from the later points. This deviation was attributed largely to the mixing process. Injection of acetone, which is almost negligibly hydrated in aqueous solution,[6] gave a comparable amount of excessive absorbance for about 5 s before the absorbance became essentially constant. The initial absorbance was obtained by extrapolation to zero time using the first-order rate equation and points taken after 5 s.[7] The part of the reaction thus neglected in these extrapolations ranged from the first 3.3% at 1.4 °C to the first 48% at 59.7 °C. The ratio A_∞/A_0 was taken to equal the fraction of ketone that is unhydrated at equilibrium.

$$\underset{C}{(MeOCH_2)_2CO} + H_2O \rightleftharpoons \underset{H}{(MeOCH_2)_2C(OH)_2} \qquad (2)$$

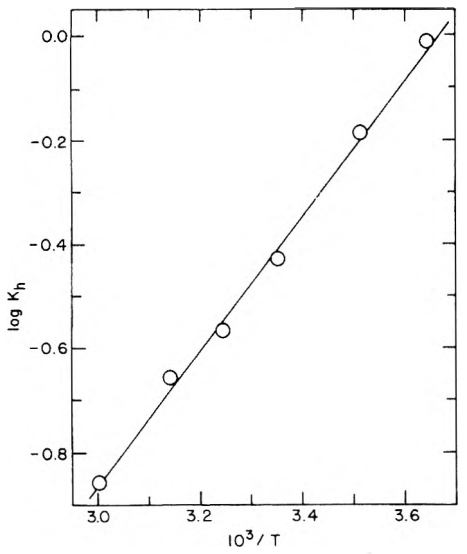


Figure 1. Plot of log K_h for the hydration of 1,3-dimethoxyacetone in aqueous solution vs. $1/T$.

Table I. Equilibrium Constants for Hydration of 1,3-Dimethoxyacetone in Aqueous Solution

Temp, °C	K_h	Standard deviation
1.4	0.975	0.013
11.5	0.652	0.010
25.0	0.373	0.003
35.0	0.271	0.004
45.1	0.219	0.002
59.7	0.139	0.006

Thus, using the symbols for the carbonyl and hydrate forms shown in eq 2, the dimensionless equilibrium constant for hydration may be expressed as shown in eq 3.

$$K_h = \frac{H}{C} = \frac{A_0}{A_\infty} - 1 \quad (3)$$

Values of K_h obtained by injecting ketone into distilled water at various temperatures are listed in Table I and plotted logarithmically against $1/T$ in Figure 1. A least-squares calculation gave a ΔH value of -5.93 ± 0.1 kcal/mol and a ΔS value of -21.7 ± 0.3 eu, where the ± figures are standard deviations. The uncertainty in these values is probably significantly larger than the standard deviations, which take no account of systematic errors, errors that are linear in $1/T$, etc.

Kinetics of Hydration. At 25 °C 66 runs were made using cacodylic acid (HCa) buffers at ionic strength 0.289 over the pH range 5.13–7.32. The k_{obsd} values were fit to eq 4

$$k_{obsd} = k_H[H^+] + k_{HCa}[HCa] + k_{Ca}[Ca] + k_h[OH^-] + k_w \quad (4)$$

which allows for general acid and base catalysis. Except for k_H, which was zero, the values obtained are listed in Table II. They fit the k_{obsd} values with a standard deviation of 3.2%. Since the k_h term is seen never to have contributed more than 4% to the overall reaction, and since the k_h value obtained is slightly smaller than its standard deviation, no reliable information on hydroxide ion catalysis was obtained. Setting k_h equal to zero did not significantly change the values obtained for k_{HCa}, k_{Ca}, and k_w or the fit to the experimental data.

The larger rate constants obtained using the cacodylate buffers were about as large as can be measured reliably using the technique described. Experiments using somewhat more basic buffers gave reactions that were too fast to follow by this technique. Therefore, we used a stopped-flow temperature-jump kinetic method, which could be applied to much more basic solutions. To make hydroxide ion catalysis dominant, the buffer base used was triethylamine, which is strongly basic but rather hindered. To minimize the effects of side reactions that degrade dimethoxyacetone in basic solutions, the temperature was jumped (from an initial 20 °C) within 2 s after stopped-flow mixing. The average final temperature, calculated from the magnitude of the overall change in absorbance and ΔH for hydration, for each of the buffers used was in the range 27 ± 3 °C. The variations of rate in this small range were obscured by the fairly large uncertainties in the rate constants obtained; standard deviations ran around 20% of the values of the constants. The results obtained are listed in Table III, where each observed rate constant is the average of at least five runs. In a least-squares fit of the data to eq 5

$$k_{obsd} = k_b[Et_3N] + k_h[OH^-] + k_w \quad (5)$$

k_w was assumed to have the value listed in Table II. From the values 3240 ± 230 and 3 ± 4 M^{-1} s^{-1} obtained for k_h and k_b, respectively, the first-order rate constants in the last column of Table III were calculated. No more than 5% of any of these values arose from the k_b term. This fact and the large standard deviation show that we have obtained no more than a rough upper limit for k_b. It is plausible that the catalysis constant for triethylamine should be so much smaller than that for hydroxide ions. The relative catalytic activities would be expected to be similar to those for the mutarotation of sugars. If the catalysis constant for triethylamine fits the Bronsted equation for the mutarotation of glucose at 18 °C given by Bell[9] it will be smaller than that for hydroxide ions by 620-fold. Steric hindrance, which has been observed in sugar

Table II. Catalysis Constants for Hydration of 1,3-Dimethoxyacetone in Water at 25 °C [a]

Constant	Value[b]	Max % contribution[c]
k_{HCa}	0.065 ± 0.004	45
k_{Ca}	0.296 ± 0.009	75
k_w	0.0185 ± 0.0006	48
k_h	5400 ± 5500	4

[a] At ionic strength 0.289. [b] These rate constants, for approach to equilibrium, are in M^{-1} s^{-1}, except for k_w, which is in s^{-1}. The ± figures are standard deviations. [c] To k_{obsd}.

Table III. Hydration of 1,3-Dimethoxyacetone in the Presence of Triethylamine Buffers [a]

$[Et_3N]_t$,[b] M	pH	Ionic strength[c]	k^d, s^{-1} Obsd	k^d, s^{-1} Calcd
0.0125	10.55	0.013	1.61	1.32
0.0200	10.59	0.020	1.43	1.50
0.0250	10.47	0.025	1.56	1.17
0.0345	10.52	0.035	1.42	1.34
0.0450	10.56	0.045	1.48	1.50
0.0375	10.615	0.101	1.71	1.80
0.0500	10.615	0.101	1.92	1.82
0.0750	10.67	0.101	1.89	2.09
0.1000	10.63	0.101	1.99	1.96
0.0250	10.945	0.101	3.9	3.8
0.0500	10.965	0.101	3.8	4.0
0.1000	11.08	0.102	4.0	5.3
0.1000	11.505	0.104	13.0	13.8

[a] In aqueous solution at 27 ± 3 °C. [b] Sum of protonated and unprotonated amine concentrations. [c] Sodium chloride added as needed to reach the ionic strength shown. [d] First-order rate constants for approach to equilibrium.

mutarotations[10] and in catalysis by triethylamine,[11] should make the constant still smaller.

Acidity of the Ketone Hydrate. The acidity of the hydrate was determined by a method like that used previously for isobutyraldehyde,[12] in which the absorbance in the presence of sodium hydroxide is compared with the absorbance in neutral solution. The ketone and sodium hydroxide solutions were mixed by use of a stopped-flow spectrophotometer and "initial" absorbances (after ~0.3 s) measured. Under such conditions the hydration–dehydration equilibrium is reached as is equilibrium in the acid–base reaction (eq 6)

$$(MeOCH_2)_2C(OH)_2 + OH^- \overset{K_{h^-}}{\rightleftharpoons} (MeOCH_2)_2C(OH)O^- \quad (6)$$

but complications from slower processes, such as aldolization, which become important only after several seconds, are negligible. The presence of sodium hydroxide uses up some of the hydrate via eq 6, and some of the ketone is then used up in restoring the hydration–dehydration equilibrium. Values of K_{h^-} were calculated from eq 7

$$K_{h^-} = \frac{(D_0 - D)(K_h + 1)}{DK_h[OH^-]_e} \quad (7)$$

where D_0 is the absorbance of a neutral solution of ketone and D is the absorbance in the presence of the equilibrium concentration of hydroxide ion $[OH^-]_e$, corrected for a small amount of absorption by the sodium hydroxide solution. A K_{h^-} value of 6.8 with a standard deviation of 1.1 was obtained at 25 °C. This corresponds to a pK_a value of 13.17 ± 0.07 for the hydrate.

Equilibrium in Bisulfite Addition. The apparent equilibrium constant for the formation of total bisulfite addition compound from total ketone and total sulfite is defined in eq 8

$$K_{app} = \frac{[\text{adduct}]_t}{[\text{ketone}]_t[\text{sulfite}]_t} \quad (8)$$

in which the subscript t's refer to all states of protonation and of hydration. Most of the values of K_{app} at 25 °C in the pH range 2.5–10.0 were obtained by dissolving the crystalline sodium bisulfite addition compound of the ketone in water and determining the extent of dissociation by quenching in cold acid and titrating the bisulfite formed iodometrically. Below pH 8.5 the equilibrium concentration of adduct was simply equal to the initial concentration minus the concentration of sulfite formed by dissociation. Above this pH, however, base-catalyzed oxidation by the traces of oxygen present, even though the experiments were carried out under nitrogen, removed some of the sulfite formed. Therefore, between pH 8.5 and 10.0 after the acid-quenched solution had been titrated to determine the concentration of sulfite formed by dissociation, excess iodine and sodium borate were added. At the resultant pH (~8) the adduct dissociated rapidly and the sulfite reacted with iodine. From the amount of excess iodine remaining the concentration of adduct could be determined. Above pH 10 the bases present in the solution interfered with the acid-quenching process (as had been observed previously in the case of isobutyraldehyde[12]). Base-catalyzed reactions of the ketone also appeared to give complications, especially in the higher part of this pH range. Therefore K_{app} values were measured by stopped-flow experiments using the ketone in one mixing syringe and a borate buffer or sodium hydroxide solution in the other. Equilibrium is rapidly established at these pH's, and absorbances at the ketone absorption maximum obtained after a few seconds remained constant for several minutes or more. After correction for small amounts of absorbing species in the sulfite solutions, these absorptions were used to calculate ketone and then adduct and sulfite concentrations. The plot of log K_{app} vs. pH in Figure 2 shows that the values obtained spectrophotometrically in the pH range 7–10 agree satisfactorily with those obtained titrimetrically.

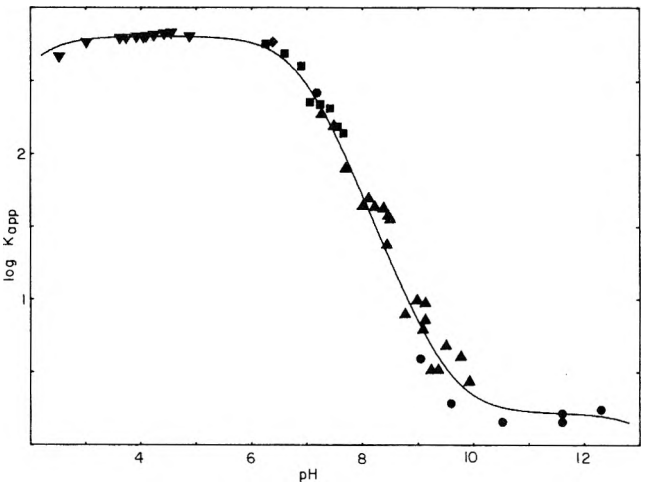


Figure 2. Plot of log K_{app} for addition of bisulfite to 1,3-dimethoxyacetone. Values were determined titrimetrically using acetate (▼), phosphate (♦), cacodylate (■), and borate (▲) buffers, and by stopped-flow spectrophotometry using borate buffers (●).

To express K_{app} in terms of more fundamental constants, we have assumed that all unicharged ions have the same activity coefficient γ and that the activity coefficient of a doubly charged ion is equal to γ^4. If the equilibrium constants for addition of bisulfite and sulfite ions to the ketone are denoted K_{SH} and K_{S2}, respectively

$$K_{SH} = [R_2C(OH)SO_3^-]/([R_2CO][HSO_3^-]) \quad (9)$$

$$K_{S2} = [R_2C(O^-)SO_3^-]/([R_2CO][SO_3^{2-}]) \quad (10)$$

then K_{app} may be expressed as shown in eq 11

$$K_{app} = \frac{K_{SH} + K_{S2}K_{HSO_3}/([H^+]\gamma^4)}{[1 + K_h + K_hK_{h^-}K_w/([H^+]\gamma^2)][1 + [H^+]\gamma^2/K_{SO_2} + K_{HSO_3}/([H^+]\gamma^4)]} \quad (11)$$

in which K_{SO_2} and K_{HSO_3} are the first and second ionization constants of "sulfurous acid", K_w is the autoprotolysis constant of water, and K_h and K_{h^-} were defined in eq 3 and 6. Values of K_{SH}, K_{S2}, and pK_{HSO_3} were calculated so as to minimize the sum of the square of (log K_{obsd} − log K_{calcd}), with γ values calculated from the Davies equation.[13] The values obtained for K_{SH}, K_{S2}, and pK_{HSO_3} were 880 ± 56 M^{-1}, 2.26 ± 0.24 M^{-1}, and 7.31 ± 0.05, respectively, where the ± figures are standard deviations. The line in Figure 2 was based on these values and an ionic strength of 0.1. The deviations of the points from the line arise in part from the fact that they represent measurements at ionic strengths ranging from 0.026 to 0.159. The pK_{HSO_3} value is fairly close to the literature values 7.205 and 7.30.[14]

The slight decrease in K_{app} below pH 3 arises from the transformation of some of the bisulfite ions to sulfur dioxide (pK_{SO_2} = 1.89[14]). The decrease that occurs on going above pH 6 arises from the transformation of bisulfite ions to sulfite ions. The decrease is halted as the hydroxylic hydrogen atom of the bisulfite addition compound becomes largely ionized above about pH 10. In fact, the ionization constant K_a for this hydrogen may be expressed as shown in eq 13. Our results give a pK_a value of 9.89.

$$K_a = [H^+][R_2C(O^-)SO_3^-]/[R_2C(OH)SO_3^-] \quad (12)$$

$$K_a = K_{HSO_3}K_{S2}/K_{SH} \quad (13)$$

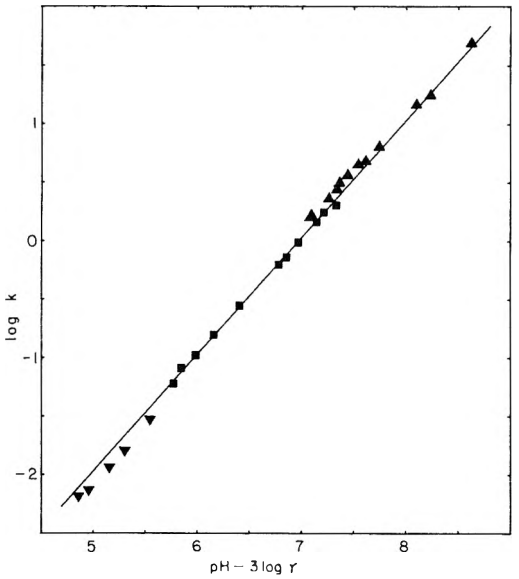


Figure 3. Plot of log k_{obsd} for the dissociation of the sodium bisulfite addition compound of 1,3-dimethoxyacetone in acetate (▼), cacodylate (■), and borate (▲) buffers vs. pH − 3 log γ.

Kinetics of Decomposition of the Bisulfite Adduct. The rate of decomposition of the bisulfite addition compound of the ketone was studied by stopped-flow spectrophotometric measurements in the presence of excess potassium triiodide, which reacts with the sulfite as soon as it is formed. The solutions were buffered and first-order rate constants were calculated from eq 14.

$$k_{obsd}t = \ln[([I_3^-]_0 - [I_3^-]_\infty)/([I_3^-] - [I_3^-]_\infty)] \quad (14)$$

If the reaction proceeds by rate-controlling decomposition of the conjugate base of the reactant as shown in eq 15 and 16

$$R_2C(OH)SO_3^- \overset{K_a}{\rightleftharpoons} H^+ + R_2C(O^-)SO_3^- \quad (15)$$

$$R_2C(O^-)SO_3^- \xrightarrow{k_d} R_2CO + SO_3^{2-} \quad (16)$$

the observed first-order rate constant may be expressed as shown in eq 17

$$k_{obsd} = k_dK_a/(\gamma^3 a_{H^+}) \quad (17)$$

where γ is the activity coefficient of a singly charged ion. To test this mechanism values of log k_{obsd} obtained using borate, cacodylate, and acetate buffers are plotted against pH − 3 log γ in Figure 3. (The pH never got close enough to pK_a for any significant fraction of the reactant to be present as the dianion.) The standard deviation of the 28 log k_{obsd} values from the line shown, which is based on the least-squares best k_dK_a value of $(1.08 \pm 0.18) \times 10^{-7}$ M s^{-1}, is 0.072. We regard this agreement as satisfactory, but the systematic nature of some of the deviations from the line suggests that the reaction may be subject to general base catalysis. Since the three significant bases present are all unicharged anions, general base catalysis gives eq 18

$$k_{obsd} = (k_dK_a/(\gamma a_{H^+}) + k_b[B^-] + k_{Ca}[Ca] + k_a[A^-])/\gamma^2 \quad (18)$$

in which A^- is acetate, B^- is borate, and Ca is cacodylate. (The first term in the equation corresponds to hydroxide ion catalysis; experiments in strongly acidic solution showed that the uncatalyzed reaction is negligible.) Least-squares treatment minimizing the sum of the squares of (log k_{obsd} − log k_{calcd}) gave values of $(9.00 \pm 0.26) \times 10^{-8}$ M s^{-1}, 355 ± 45 M^{-1} s^{-1}, 0.11 ± 0.04 M^{-1} s^{-1}, and zero for k_dK_a, k_b, k_{Ca}, and k_a, respectively, where the ± figures are standard deviations. These values gave log k_{calcd} values that fit the observed data with a standard deviation of 0.043. Although general base catalysis contributed as much as 34% to the overall reaction in the most favorable case, according to these rate constants, we do not regard it as definitively established. We did not make the systematic changes in concentration that would have been made in a study of general base catalysis, since we were just interested in the value of k_dK_a. Activity coefficients of doubly charged ions tend to deviate from activity coefficient equations at rather low ionic strengths. Perhaps the deviations from eq 17 seen in Figure 3 arise largely from this and other sources rather than from general base catalysis.

Combination of the k_dK_a values of 9×10^{-8} M s^{-1} with the pK_a value 9.89 gives a k_d value of 706 s^{-1}, which, when multiplied by K_{S2}, gives a k_c value of 1599 M^{-1} s^{-1}.

Equilibrium Constant for Hydration from Measurements Using Bisulfite. The preceding observations show that bisulfite ions have a rather large equilibrium constant for addition to dimethoxyacetone and that the addition reaction is much faster than hydration of the ketone around pH 6 or 7 (unless sulfite or bisulfite ions are unexpectedly good catalysts for hydration). These facts gave the basis for an independent way to determine the equilibrium constant for hydration. Aqueous sodium bisulfite and a phosphate buffer were put in one syringe and an aqueous solution of the ketone in the other syringe of the stopped-flow spectrophotometer. Very quickly after mixing, the absorbance at the carbonyl maximum decreases, reaching a minimum at time t_1 because part of the free ketone has been transformed to the equilibrium concentration of its bisulfite addition compound, but very little of the ketone hydrate has had time to lose water to replenish the supply of free ketone. As the concentration of bisulfite used is increased the concentration of free ketone present at time t_1 decreases. If the equilibrium constant for bisulfite addition were very large (>10^6 M^{-1}) the concentration of free ketone at time t_1 would essentially drop to zero when the bisulfite concentration became equal to the concentration of free ketone before reaction with bisulfite. Our equilibrium constant is not this large, but it is large enough to permit us to change the concentrations of reagents and, in essence, extrapolate to the situation that would prevail if the equilibrium constant were infinitely large. If, as previously, C represents the free ketone and f is defined as the fraction of C initially present that remains at time t_1

$$f = \frac{C_1}{C_0} \quad (19)$$

then K_{app} may be expressed as shown in eq 20

$$K_{app} = \frac{1 - f}{([HSO_3^-]_0 - (1 - f)C_0)f} \quad (20)$$

where the subscript zeros refer to concentrations before bisulfite addition begins. The initial free ketone concentration C_0 may be set equal to the total ketone concentration C_t (free and hydrated) divided by $1 + K_h$. Algebraic manipulation then gives eq 21

$$f[HSO_3^-]_0/(1 - f) = 1/K_{app} + fC_t/(1 + K_h) \quad (21)$$

which shows that a plot of $f[HSO_3^-]_0/(1 - f)$ vs. fC_t should give a straight line of slope $1/(1 + K_h)$ and intercept $1/K_{app}$. Data obtained at 25 °C and pH 6.4, using concentrations that varied f from 0.24 to 0.84, are plotted in Figure 4. The intercept and the slope give values of 688 M^{-1} and 0.362 for K_{app} and K_h, respectively. The latter value agrees well with the equilibrium constant for hydration at 25 °C listed in Table I, but eq 11 and our values of K_{SH}, K_{S2}, and K_{HSO_3} give a K_{app} value at pH 6.4 and ionic strength 0.16 that is 29% smaller than

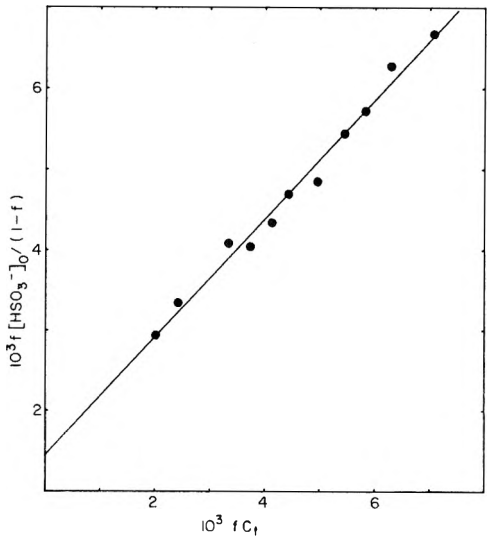


Figure 4. Plot for determination of the equilibrium constants for hydration (K_h) and bisulfite addition (K_{app}) by 1,3-dimethoxyacetone from stopped-flow spectrophotometric measurements.

the value obtained by these measurements. Calculations suggest that this deviation arises partly because the rate of establishment of the sulfite adduct equilibrium is not quite fast enough to make hydration of the aldehyde formed at time t_1 completely negligible.

Discussion

Hydroxide ions are assumed to catalyze the hydration of aldehydes and ketones simply by rate-controlling addition to the carbonyl carbon atom. The rate constant for such addition to dimethoxyacetone is then equal to k_h, the hydroxide ion catalysis constant for approach to equilibrium, multiplied by $K_h/(1 + K_h)$. This rate constant has been used in Figure 5, which contains extended Bronsted plots[2] for the additions of hydroxide and sulfite ions to aldehydes and ketones (eq 22).

$$R_2CO + N \overset{K_c}{\rightleftharpoons} R_2CO^- \quad (22)$$
$$\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\quad N$$

The data on addition of sulfite to benzaldehyde are from the work of Kokesh and Hall[15] and refer to 21 °C and ionic strength 1.0, instead of 25 °C and ionic strength zero like the other values. The data on sulfite addition to dimethoxyacetone are from the present work; the other data on sulfite addition,[16] addition of hydroxide ions to isobutyraldehyde,[12] and additions of hydroxide ions to other aldehydes and ketones[2] are also from the literature. The additions to dimethoxyacetone are seen to be slower than similar additions to aldehydes that have about the same equilibrium constants. It was noted previously that steric hindrance, as seen, for example, in the reactions of ortho-substituted triarylmethyl cations, produces such deviations in extended Bronsted plots.[2] In such cases steric effects are larger in the transition state than in the product, or, at least, a larger fraction of the equilibrium steric effects than of the equilibrium polar effects have appeared at the transition state. We believe that the deviations of the points for dimethoxyacetone from the lines roughly described by the points for the other compounds are probably largely steric in origin. Since there is a tendency for substituents to become smaller on moving to the right in Figure 5, these lines would probably have smaller slopes if steric effects were held constant.

It is interesting that the ratio of the equilibrium constant for addition of sulfite to the equilibrium constant for addition

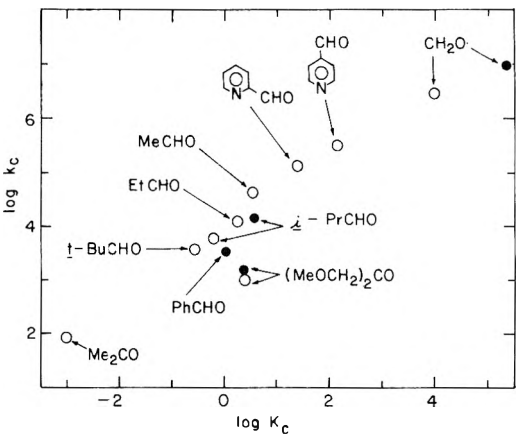


Figure 5. Rate–equilibrium plot for the addition of hydroxide ions (open circles) and sulfite ions (solid circles) to aldehydes and ketones in aqueous solution at 25 °C.

of hydroxide ions decreases steadily as hydrogen attached to the carbonyl group is replaced by alkyl or substituted alkyl groups. Thus log K_{SO_3} − log K_{OH} decreases from 1.35 for formaldehyde to 0.78 for isobutyraldehyde to −0.05 for dimethoxyacetone. The ratio of *rate* constants, however, decreases much more slowly, log k_{SO_3} − log k_{OH} being 0.53, 0.37, and 0.26 for formaldehyde, isobutyraldehyde, and dimethoxyacetone, respectively. Relatively constant values are required by the Ritchie equation (eq 23)

$$\log k = \log k_0 + N_+ \quad (23)$$

which was originally applied to the combination of nucleophilic reagents with triarylmethyl and diazonium cations,[17,18] but has since been applied to attack on the carbonyl carbon atom of esters.[19] In eq 23 the value of N_+ depends on the nature of the nucleophile, the solvent, and the temperature, but not on that of the electrophile; k is the second-order rate constant for combination of the nucleophile and electrophile; and the value of k_0 depends only on the nature of the electrophile. Therefore, log k_{SO_3} − log k_{OH} for reaction with any electrophile should just be equal to $(N_+)_{SO_3} - (N_+)_{OH}$, a constant. However, our values are 0.40 ± 0.14 instead of 7.90 − 4.75, or 3.15, as they should be according to the latest set of N_+ values.[19] Ritchie has noted other large deviations from eq 23 by the hydroxide ion and suggested that hydroxide ions are acting as general base catalysts of the reaction of water, removing a proton from water as its oxygen atom forms a bond to carbon.[19] Since hydroxide ion is the only base whose direct reaction with an electrophile gives the same product as the base-catalyzed reaction of water, these two alternative reaction paths in aqueous solution can be more readily distinguished with other bases. For this reason we plan to include data on a wide variety of nucleophiles in a forthcoming more general discussion of rate–equilibrium correlations in Lewis acid–base reactions.

Experimental Section

1,3-Dimethoxyacetone. The ketone was prepared by oxidation of 1,3-dimethoxy-2-propanol, which was made from epichlorohydrin and sodium methoxide by a method analogous to that of Abouzeid and Linnell.[20]

One procedure, which was not entirely reproducible, used the complex of chromium trioxide and pyridine.[21-23] In a typical run the complex from 160 g of chromium trioxide was dissolved in 2 l. of methylene chloride at 0 °C and 27 g of 1,3-dimethoxy-2-propanol added with stirring over a period of 10 min. After 10 min more the precipitate that formed was separated and washed with methylene chloride and the combined methylene chloride solutions concentrated and then vacuum distilled to give 12 g (45%) of 1,3-dimethoxyacetone: bp 89–90 °C (40 mm); 99.9% pure by GLC; ir 2990, 2985, 2930, 2910,

2820, 1740 (C=O), 1470, 1450, 1280, 1205, 1180, 1135, 1110, 1050, 990, and 950 cm^{-1}. 1,3-Dimethoxyacetone has been reported to boil at 78.0–78.5 °C (18 mm),[24] 62.5–63.0 °C (10 mm),[25] and 71.0–71.5 °C (16 mm),[26] but no spectral data seem to have been reported. ^1H NMR[27] ($CDCl_3$) δ 3.43 (s, 6, CH_3) and 4.18 ppm (s, 4, CH_2). The ^1H NMR spectrum in D_2O showed peaks at δ 3.40, 3.44, 4.30, and usually one at 3.39 ppm (relative to sodium 4,4-dimethyl-4-silapentane-1-sulfonate). The three (or two) peaks in the δ 3.39–3.44-ppm region were not sufficiently well resolved to measure their separate areas reliably, but their combined areas were about 2.23 times that of the peak at 4.30 ppm (at a probe temperature of about 40 °C). In a number of runs thought to have been carried out in the same way, the purity of the product was much poorer (sometimes, but not always, because of unoxidized starting material) or the yield was much lower.

The Moffatt–Pfitzner oxidation using *N,N'*-dicyclohexylcarbodiimide in dimethyl sulfoxide[28] was more reproducible. However, if no excess of dimethyl sulfoxide was used the product contained starting alcohol, and if more than about a 5% excess was used the product contained dimethyl sulfoxide. We could not remove much of either of these impurities by fractional distillation. In a typical successful run 24 g (0.20 mol) of alcohol, 120 g (0.58 mol) of *N,N'*-dicyclohexylcarbodiimide, 15 ml (0.21 mol) of dimethyl sulfoxide, and 3 ml of anhydrous phosphoric acid in 200 ml of methylene chloride were shaken in a 500-ml Erlenmeyer flask equipped with a drying tube. Occasional GLC analysis showed that reaction was complete in 5 days. Dicyclohexylurea and methylene chloride were removed by filtration and distillation, respectively. Distillation of the remaining liquid through a Vigreux column at 20 mm gave three fractions, all boiling at 82–83 °C. The middle 8-g fraction was 99.5% pure by GLC and the first (~5 g) and last (~2 g) fractions were somewhat less pure.

Some samples of ketone, upon standing for a few days, even in a freezer, acquired large amounts of impurities—sometimes white crystals separated. Other samples were rather stable to storage.

Kinetics of Ketone Hydration. A typical run below pH 9 was started by injecting 4 μl of ketone into 3 ml of aqueous solution from a 10-μl Hamilton syringe into a square topped 1-cm quartz cell in the thermostated cell compartment of a Cary spectrophotometer, Model 16. The syringe fit in the hole in a neoprene stopper, which fit through a hole in the top of the cell compartment into the top of the cell and kept light out of the cell compartment. The bottom of the cell contained a small Teflon-covered magnetic stirring bar, which was driven by a magnet in a motor below the cell.[5]

The runs above pH 9 were carried out using a Durrum-Gibson stopped-flow spectrophotometer with temperature-jump attachment. A 0.0055 M aqueous solution of dimethoxyacetone was put in one of the mixing syringes and a triethylamine buffer solution (made from recrystallized triethylamine hydrochloride and sodium hydroxide solution with sodium chloride added in some cases) was put in the other. Two seconds after stopped-flow mixing the capacitor, charged to 3.5 kV, was discharged for 0.1 s to heat the contents of the cell. The absorbance values at 275 nm were read starting 0.4 ms after the heating pulse ended. Over a period of time long enough to permit the absorbance to reach a maximum (and then decrease as the cell cooled), 4096 absorption values at constant time intervals were read into a Nicolet digital storage oscilloscope, Model 1090. Every 40th value was then transferred to the memory of an interfaced Hewlett-Packard calculator, Model 9830. A stored program then selected 20 values spaced as uniformly as possible in absorbance units between the minimum and maximum absorbances and used a nonlinear least-squares method[29] to calculate best values for the first-order rate constant, the infinite absorbance, and the change in absorbance.

The pH of solutions of dimethoxyacetone in triethylamine buffers tends to drift with time. The values listed in Table III were read as quickly as possible (about 1 min) after making solutions identical with those mixed in the temperature-jump experiments. The results deviated from those calculated on the basis of the known composition of the buffers and the pK_a of triethylammonium ions (10.67)[30] by an average of 0.068.

Determination of the Acidity of 1,3-Dimethoxy-2,2-propanediol. The acidity constant of the hydrate of 1,3-dimethoxyacetone was determined by stopped-flow spectrophotometric measurements in which an aqueous solution of dimethoxyacetone was in one of the two mixing syringes and aqueous sodium hydroxide in the other. The solutions used were of such strengths as to give sodium hydroxide concentrations of 0.12–0.58 M and total ketone concentrations (in all forms) of 0.003–0.009 M. The sodium hydroxide solutions used had an apparent extinction coefficient of 0.016 M^{-1} cm^{-1} and the apparent extinction coefficient of the ketone–hydrate equilibrium mixture at 25 °C is 16.1 M^{-1} cm^{-1}. In 23 runs an average K_h- value of 6.8 M^{-1} and a standard deviation of 1.1 M^{-1} were obtained. After some initial small variations that were attributed to the mixing process the absorbance remained constant for several seconds, after which a slow increase could be noted. The absorbance values used were measured at about 0.3 s.

Equilibrium Constants for Addition of Sodium Bisulfite to 1,3-Dimethoxyacetone. Equilibrium in addition of bisulfite to the ketone was studied in a manner similar to that reported earlier for addition to isobutyraldehyde.[16] Most of the runs carried out below pH 10 were approached from the side of the bisulfite addition compound. In a typical preparation of the addition compound the distillate (which contained ketone and dimethyl sulfoxide) from the Moffatt–Pfitzner oxidation of 24 g of 1,3-dimethoxy-2-propanol by 50 ml of dimethyl sulfoxide was dissolved in 50 ml of methanol and 1 ml of pyridine. Addition of 20 g of sodium bisulfite was followed by heating to boiling, filtration, and removal of methanol from the filtrate under vacuum. Recrystallization of the resulting white powder from 95% ethanol and 8 h vacuum drying at room temperature gave 15 g of addition compound. Addition of weighed samples to ice-cold 0.5 M hydrochloric acid followed by iodometric titration showed that 1.6 ± 0.3% sodium bisulfite was present. Addition of sodium borate (to pH ~8) then liberated more sulfite whose iodometric titration showed that 76.6 ± 0.7% of sodium bisulfite addition compound was present. The remaining ~21% of the sample was assumed to be water and sodium sulfate. (Other bisulfite addition compounds are known to form hydrates from which water is not easily removed at room temperature.)[16]

A typical determination of K_{app} in the pH region 8.5–10.0, where the total amount of sulfite and adduct present was determined by two titrations rather than from the amount of adduct weighed out, was carried out as follows. Solutions of weighed amounts of the bisulfite addition compound were mixed under nitrogen with standard borate buffer solutions in a flask that was allowed to reach thermal equilibrium in a 25.0 °C constant temperature bath, where kinetic studies show that chemical equilibrium is reached in seconds in this pH range. Addition to ice-cold hydrochloric acid and titration gave the amount of free sulfite present and addition of sodium borate and retitration gave the amount that had been tied up as adduct.

When K_{app} was determined by a stopped-flow spectrophotometric measurements above pH 9 the absorbance of mixtures of ketone and buffer in the absence of sulfite was compared with the absorbance in the presence of sulfite.[16] This procedure was necessitated by the rapidity of the reaction. In the runs at pH 7.175, however, the reaction was slow enough that the initial absorbance (before any appreciable reaction) could be compared with the equilibrium absorbance.

Kinetics of the Decomposition of the Bisulfite Addition Compound. The kinetics of the decomposition of the sodium bisulfite addition compound of 1,3-dimethoxyacetone were followed in the same way that has been described for isobutyraldehyde.[16] Ionic strengths were around 0.10 for the acetate and cacodylate buffers and 0.01 for the borate buffers. Each run was carried out in triplicate.

Simultaneous Determination of K_{app} and K_h. In this method about 0.017 M 1,3-dimethoxyacetone was put in one stopped-flow syringe and a solution 0.0025–0.018 M in sodium bisulfite and 0.1589 M in total phosphate buffer in the other. Upon mixing the transmittance initially rapidly increased and then much more slowly decreased. The maximum values were read at about 1 s. The pH of the solutions was 6.406 ± 0.026.

Acknowledgment. We are indebted to Dr. William H. Sachs for creating the interface and computer program to use the HP 9830 calculator for stopped-flow and T-jump kinetics, and to Mrs. Karen Wang for making some of the calculations.

Registry No.—1,3-Dimethoxyacetone, 18664-32-9; 1,3-dimethoxy-2-propanol, 623-69-8; 1,3-dimethoxy-2,2-propanediol, 59907-40-3; sodium bisulfite, 7631-90-5.

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Selectivity in Cycloadditions. 5. Cycloadditions of Nitrile Oxides to Furan. Competing Mechanisms and Regiochemistry[1]

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Generation of benzonitrile oxide (BNO) in a large excess of furan gave a 91% yield of two regioisomeric monocycloadducts **1** and **2** in a 97:3 ratio and a 1% yield of the 1,3-addition product, **3**. The primary products can react further with BNO giving cycloaddition and fragmentation products, whose structures were established through spectroscopic evidence and chemical transformations. The cycloaddition with 2-methylfuran and cycloadditions of mesitonitrile oxide and *p*-nitro- and *m*-nitrobenzonitrile oxides to furan are also reported. Frontier orbital considerations allowed elucidation of the regiochemistry of the cycloadditions. A competing pathway stabilized by secondary orbital interactions is suggested for the formation of the 1,3-addition product.

In previous papers of this series we have evaluated the influence of polar and steric effects[3] as well as of π-conjugation[4] on nitrile oxide[5] cycloadditions. Although π-conjugation was remarkably effective in directing the regioselectivity of cyclopentadiene cycloadditions, nevertheless the two possible [4 + 2] cycloadducts of the dipole could be isolated. The results support the frontier orbital treatment of 1,3-dipolar cycloadditions,[6] which has recently led to a satisfactory understanding of regioselectivity and periselectivity phenomena.

Since the five-membered ring heteroaromatics, such as furan, thiophene, and pyrrole, have, in spite of their aromaticity, frontier orbital energies and shapes similar to those of cyclopentadiene[7]—which may be viewed as a cyclic diene aromatically stabilized through hyperconjugation[8]—it seemed to us interesting to extend our study to their dipolarophilic activities. A vast amount of material is available concerning the reactivity of heteroaromatics in substitution reactions[9] or in cycloadditions where the heteroaromatics enter as $_{\pi}4_{s}$ components,[10] but the study of their dipolarophilic activities has been relatively scanty to date. A second aim of the studies was based on the well-known propensity of heteroaromatics toward substitution rather than addition reactions. If diradical or zwitterionic intermediates with a finite lifetime are ever involved in cycloaddition reactions, they would be expected to convert easily, perhaps quantitatively, to the substitution products because of the gain of aromaticity.

We have already given an account of the reactions of furan with nitrile oxides[11] and nitrile imines.[12] In this paper we report a more detailed study of the cycloaddition of nitrile oxides to furan, with particular attention directed at the regiochemistry of the reaction and to the detection of the substitution products.

Results

Furan is very slightly reactive toward nitrile oxides. Only the in situ preparation of benzonitrile oxide (BNO) in furan as solvent permitted isolation of a complex mixture of cycloadducts along with considerable amounts of diphenylfuroxan, the dimer of BNO, as well as 3,5-diphenyl-1,2,4-oxadiazole.

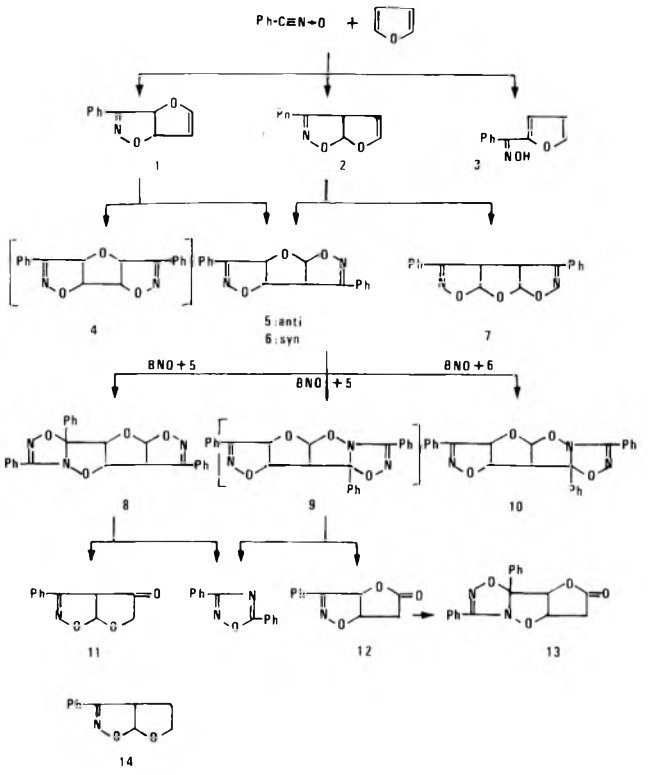
Because of the low reactivity of furan the primary monoadducts **1** and **2**, which have a reactive enol ether moiety,[6b,d] compete efficiently for BNO, even when furan is used as solvent. BNO also adds sluggishly on the C=N isoxazoline bonds of the bis adducts.

Chromatographic and fractional crystallization procedures led to isolation and characterization of not less than ten compounds. These products will be examined separately, depending upon whether they are 1:1 mono adducts or are derived from 2 mol of BNO and 1 mol of furan (bis adducts) or are further addition or transformation products.

Mono Adducts. On performing the reaction with a very small concentration of BNO (10^{-2} M) in furan in order to suppress any further reactions of the primary products, we obtained a 91% yield of the two cycloadducts **1** and **2** in a 97:3 ratio, and a 1% yield of the oxime **3**, as determined by GLC. In the normal runs (see Experimental Section) column chromatography gave the mono adducts in yields of 9–12, 0.3, and 0.1–0.2%, respectively.

The structures were assigned on the basis of chemical and NMR evidence. Acidic hydrolysis of **1** gives the isoxazoline

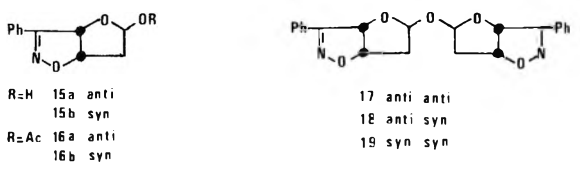
Scheme I



ring cleavage product, 2-benzoylfuran; **2** was selectively hydrogenated on the C=C bond to the known adduct of 2,3-dihydrofuran **14**,[13] whose structure has been unequivocally proven; **3** was found identical with a sample prepared according to the literature.[14] The NMR spectra of the cycloadducts (see Table I) are fully consistent with the assignments. The bridgehead protons of **1** and **2** adjacent to the C=C double bond couple with the olefinic protons. The values of these coupling constants are identical with those reported for 2,3-dihydrofuran itself.[15] It is worth noting the deshielding effect of the dihydrofuran oxygen on the adjacent bridgehead protons. These are shifted downfield by ca. 1 ppm from the range reported for 4- and 5-isoxazolinic protons.[16]

Cycloadducts decompose slowly in wet solvents, forming a mixture of products. This behavior, which complicates the separation and isolation procedures, has been studied in more detail in the case of mono adduct **1**. After standing for 1 week in chloroform, this compound gave five major products, which were isolated by column chromatography and characterized spectrally and through chemical transformations.

The product with the smallest R_f showed a hydroxyl ir band at 3445 cm^{-1} and a NMR spectrum consistent with a structure of hemiacetal **15a** and **15b**. The product epimerized very easily

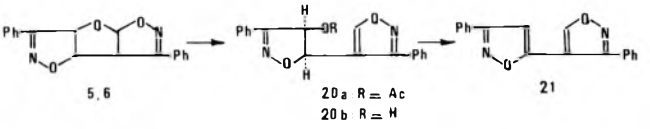


in Me_2SO/D_2O and the process could be qualitatively followed by monitoring the appearance of the doublet of the epimer at 5.94 ppm, 0.03 ppm downfield of the doublet of the C-4 isoxazoline proton. Treatment of **15** with Ac_2O/Py yielded two isomeric acetyl derivatives, whose NMR spectra are in accordance with structure **16a/16b**. The chemical shifts at the acetoxy methyls (2.04 and 1.78 ppm) are significantly different in these two compounds. The syn structure **16b** is proposed for the higher melting isomer which has the upfield methyl. The position of this resonance may be attributed to shielding by the PhC=N group of the neighboring syn isoxazolinic ring.[17]

The other four products show neither hydroxyl nor carbonyl bands in the ir spectra, and have analytical and NMR data compatible with their formulation as acetals. Three pairs of diastereomers (**17**–**19**) are therefore feasible. Two of them (**17** and **19**) possess an element of symmetry, whereas the diastereomeric pair **18** lacks any symmetry. Therefore, the structures **18** are attributed to the two lower R_f products, whose NMR spectra (see Experimental Section) show ten distinct tetrahydrofuran protons. The other two products, probably the anti–anti couple **17**, each showed only five distinct protons in the NMR, but the spectral data do not allow one to choose between the symmetrical structures **17** and/or **19** with reasonable certainty.

Bis Adducts. The main product (10–16% yield calculated from BNO) in the normal runs was the bis adduct **5**, whose structure has already been demonstrated[11] through ring cleavage with BF_3/Ac_2O, hydrolysis of the acetate **20a**, and subsequent dehydration of the alcohol **20b** to the known 3,3′-diphenyl-4,5′-diisoxazole **21**[18] (see Scheme II).

Scheme II



Two other bis adducts have now been isolated and characterized. One of them (2.3% yield) led to the same ester obtained from **5** by treatment with BF_3/Ac_2O and was therefore assigned structure **6**, stereoisomeric with **5**. Both **4** and **5** were also obtained by regioselective cycloaddition of BNO to the mono adduct **1**. Inspection of NMR spectra confirmed the assigned structures and allowed elucidation of the stereochemistry. Coupling constants between the protons in positions 3 and 4 of the central tetrahydrofuran ring are 0.0 Hz for **5** and 8.7 Hz for **6**. Reference to the Karplus equation and to analogous values for bis adducts obtained from cyclopentadiene[4] unequivocally established the anti configuration for **5** and the syn structure **6** for the minor product.

The third bis adduct **7** was isolated in a very low yield (0.6%) and was independently obtained by cycloaddition of BNO to mono adduct **2**. Its symmetrical structure appears clearly from the NMR spectrum. The four isoxazoline protons occur as two coupled (J = 4.7 Hz) doublets at 6.21 and 4.37 ppm, respectively (2 H each). An anti stereochemistry is suggested by analogy to the stereospecific formation of the corresponding anti bis adduct on cyclopentadiene, where the stereochemistry could be safely deduced from the nonequivalence of the methylene protons.[4]

Tris Adducts and Derived Compounds. Two tris adducts (3 mol of BNO + 1 mol of furan) and two lactones were also isolated from the reaction mixture.

The NMR spectrum of the most abundant tris adduct (1.2% yield) showed the tetrahydrofuran protons as two pairs of doublets, with coupling constants of 2.8 and 5.7 Hz, respectively. These values are compatible with cis coupling constants for ring protons in isoxazolidine and isoxazoline, respectively, as previous examples in the cyclopentadiene series show.[4] A very low coupling (J = 0.5 Hz) between the hydrogens on the bond joining the two heterocyclic moieties indicates an anti configuration. Thermal breakdown of the compound yielded 3,5-diphenyl-1,2,4-oxadiazole and the ketone **11**, whose structure was deduced from spectral data and from the formation of the tosylhydrazone. An attempt to obtain the mono adduct **2** by alkaline degradation[19] of this latter derivative failed. From these spectral and chemical data, structure **8** was deduced for the tris adduct.

Table I. Chemical Shifts[a] (Coupling Constants[b]) of Cycloadducts[c]

Compd	4-H[d]	5-H[d]	Other
1	6.17 d (8.5)	5.93 o (8.5, 2.1, 1.0)	Vinyl 5.34 q (2.5, 2.1); 6.57 q (2.5, 1.0)
2	4.81 o (7.8, 2.7, 2.2)	6.70 d (7.8)	Vinyl 5.20 q (2.8, 2.7); 6.48 q (2.8, 2.2)
5[e]	6.04 d (6.5)	5.33 d (6.5)	
	5.08 d (6.0)	6.45 d (6.0)	
6[e]	6.46 bd (7.8)	5.80 q (7.8, 8.7)	
	4.72 q (8.7, 6.7)	6.58 bd (6.7)	
7	4.37 m (4.7)[f]	6.21 m (4.7)[f]	
8	4.39 bd (5.7)	6.43 d (5.7)	
	5.09 d (2.8)[g]	4.90 bd (2.8)[g]	
10	5.98 d (7.0)	5.00 t (7.0)	
	4.13 q (7.0, 4.0)[g]	6.17 d (4.0)[g]	
11	4.38 d (6.4)	6.73 d (6.4)	CH_2 4.15 s
12	6.04 d (7.3)	5.32 m	CH_2 2.98 m
13	5.23 d (3.5)[g]	4.74 m[g]	CH_2 2.68 m
15[e]	5.91 d (7.3)	5.22 m	CH_2 2.20 m, CHOR 5.53 m, OH 6.18 d (3.3)
16a	5.90 d (7.3)	5.42 m	CH_2 2.53 m, CHOAc 6.37 m, CH_3 2.04 s
16b	5.93 d (7.3)	5.28 m	CH_2 2.51 CHOAc 6.45 m, CH_3 1.78 s
20a	6.55 d (7.1)	5.50 bd (7.1)	CH 8.58 bs, CH_3 1.85 s
20b[e]	5.53 d (7.1)	5.37 bd (7.1)	CH 9.05 bs
22	5.98 m	5.98 m	Vinyl 5.39 m, 6.60 m
23	5.60 d (6.3)	4.97 d (6.3)	
	4.63 d (5.5)	6.35 d (5.5)	
24	6.33 (5.3 Hz)	3.98 d (5.3)	
25	6.11 d (8.3)	5.83 m	CH_3 1.82 t (1.1), =CH 5.00 m
26	5.84 d (6.7)	5.25 d (6.7)	CH_3 1.73 s
	4.31 s		

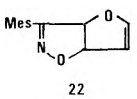
[a] Chemical shifts in parts per million (δ) from internal Me_4Si. Multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; sx, sextet; o, octet; m, multiplet; b, broad. Solvent: $CDCl_3$, unless otherwise stated. [b] In hertz. [c] Satisfactory combustion analytical data C, H, N (±0.4%) have been obtained for these compounds. Ed. [d] Numbering refers to the isoxazoline ring. [e] In Me_2SO-d_6. [f] $J + J'$. [g] Isoxazolidine ring protons.

The most abundant (1.0–1.1% yield) lactone was assigned structure **12** on the basis of spectral data (see Experimental Section) and of the hydrolytic cleavage, which yielded the known 3-phenyl-5-isoxazolylacetic acid.[20] Its reaction with BNO yielded the minor (~0.5% yield) lactone **13**, whose structure is fully consistent with spectral data. Furthermore, reaction of BNO with the bis adduct **5** yielded, along with the dimer of BNO and with some 3,5-diphenyl-1,2,4-oxadiazole, a mixture of **8**, **12**, and **13**. These latter lactones most likely originate from an unstable, nonisolated, tris adduct **9**.

The other tris adduct was isolated in 0.5% yield and was assigned structure **10**, since the same product was also obtained, along with lactone **13**, by reaction of the syn bis adduct **5** with an excess of BNO. The position of the chemical shifts of the four tetrahydrofuran ring protons as well as the lower value of the coupling constant for the isoxazolidine ring in comparison with that for the isoxazoline ring suggest the proposed structure, instead of the isomeric one, arising from an attack of BNO to the other isoxazoline ring.

Other Cycloadditions. In the reaction of furan with *p*- and *m*-nitrobenzonitrile oxides the major mono adducts could be isolated in fair yields and the regiochemistry was proven through acidic hydrolysis to the corresponding 2-nitrobenzoylfurans.[11] No attempt was made to characterize the minor products of these reactions.

Mesitonitrile oxide, a stable nitrile oxide which does not dimerize at room temperature, reacted with excess furan very slowly, but after 8 months mono adduct **22** (28%) and the bis adducts **23** (40%) and **24** (6%) were obtained. The NMR spectra show a strong resemblance to the corresponding BNO adducts.



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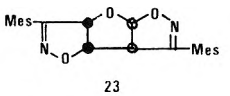
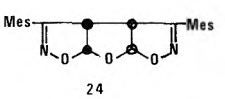
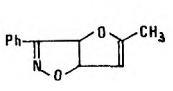


23



24



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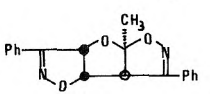
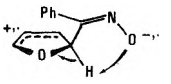


26

2-Methylfuran reacted with benzonitrile oxide to yield the mono adduct **25** as main product. Besides this minor amounts of the bis adduct **26** were isolated. Structural assignments were based on NMR spectroscopy.

Discussion

For the reaction of nitrile oxides with furan derivatives, three reaction patterns were a priori conceivable: (a) a [$_\pi 4_s$ + $_\pi 2_s$] cycloaddition of the dipole to one double bond of the ring; (b) a [$_\pi 4_s$ + $_\pi 2_s$] cycloaddition of furan to the nitrile oxide C≡N bond with possible subsequent dehydration to pyridine *N*-oxide derivative; (c) attack of the carbon atom of the nitrile oxide to the α position of furan to yield an oxime through a zwitterionic or diradical intermediate **27**.



27

Pattern b was unlikely, as previous results[4] demonstrated that conjugated dienes react as dipolarophiles rather than as dienes with nitrile oxides. As described above, the main products of the reaction with BNO were shown to be the mono cycloadducts **1** and **2** and their further addition or transformation products, consistent with the reaction pattern a. A 1% yield of the 2-benzoylfuran oxime **3**, path c, could also be detected. The cycloadducts **1** and **2** and the oxime **3** are primary products of the reaction, in the sense that they were shown to be stable and not to interconvert under the reaction conditions or during the isolation or analysis.

Taking into account the relative yields, the difference in free energy for the regioisomeric paths leading to the major cycloadduct **1** and to its regioisomer **2** could be evaluated at 2.1 kcal/mol, a value comparable to our more recent evaluations of 2.4 and 1.6 kcal/mol in the cycloadditions of BNO to cy-

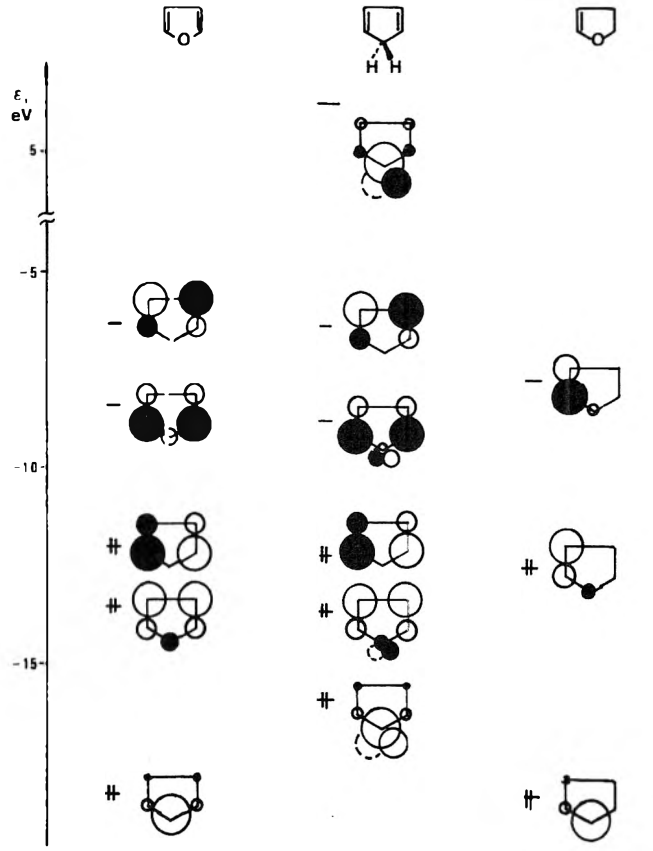


Figure 1. The π molecular orbitals of furan, cyclopentadiene, and 2,3-dihydrofuran. The radii of the circles represent the magnitudes of the atomic orbital coefficients at each center.

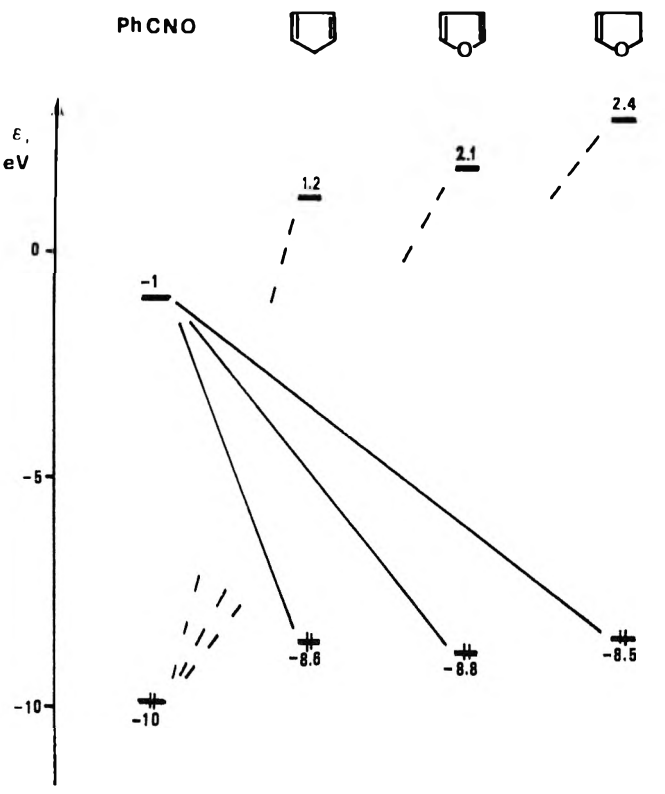


Figure 2. Interaction diagram of BNO with cyclopentadiene, furan, and 2,3-dihydrofuran.

clopentadiene and indene, respectively. The reactivity of furan is, however, reduced by a factor of 10^3 with respect to cyclopentadiene, as determined by competition experiments (see Experimental Section). A slightly lower, but comparable, regioselectivity for the reaction with mesitonitrile oxide is inferred by the isolation of bis adduct **24** in a 6% yield.

A frontier molecular orbital (FMO) treatment satisfactorily accounts for the regioselectivities observed for cyclopentadiene and furan on the one hand, and for the regiospecificity observed for the 2,3-dihydrofuran system present in the 1:1 adducts and for dihydrofuran itself[13] or the other. The shapes of the π MO's of these three dipolarophiles, as obtained from extended Hückel (EH)[21] calculations, are shown in Figure 1. The EH, CNDO/2, and MINDO/2 eigenvectors and eigenvalues for the FMO's are given in Table II. For cyclopentadiene and furan the HOMO and LUMO correspond essentially to the Ψ_2 and Ψ_3 π orbitals of butadiene. This is particularly true for the HOMO's, which have a node through the CH_2 group and oxygen, respectively. The HOMO of furan is inductively stabilized as shown by the lowest vertical IP of 8.88 eV[22] with respect to the value of 8.7 eV[7c,23] for cyclopentadiene. The LUMO of furan originates from the mixing of the Ψ_3 butadiene orbital with the p_z oxygen in an antibonding fashion, whereas in the case of cyclopentadiene, Ψ_3 mixes in the methylene π_{CH_2} and $\pi^*_{CH_2}$ orbitals out of phase and in phase, respectively. This causes nearly a cancellation of coefficient of p_z at the CH_2 group and a reinforcement of the hydrogen coefficients. As a result, the CH_2 orbital of π symmetry is mainly localized on the pair of hydrogens so that the overall shapes of the LUMO's of cyclopentadiene and furan are very similar. For dihydrofuran the shapes of the orbitals result from the influence of the oxygen donor in inducing mixing of the π and π^* orbitals of the vinyl group.[24] The IP of dihydrofuran can be estimated at 8.5 eV from the values reported for analogous enol ethers.[25]

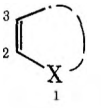
The IP and electron affinity (EA) of fulminic acid were estimated at 11 and 0.5 eV, respectively, and the empirical values of 10 and 1 eV were deduced for the π_{CNO} orbitals of BNO.[6b,c] The IP's of the dipolarophiles were discussed above and the EA's could be estimated from the $\pi \rightarrow \pi^*$ uv transitions[7b,25a] by considerations analogous to those reported.[6] The estimated orbital energies are displayed in Figure 2.

Thus the HOMO (dipolarophile)–LUMO (BNO) separation is here smaller than the other frontier orbital separation, the dipolarophiles behaving as donors and the nitrile oxides as acceptors. The nitrile oxides cycloadd in such a fashion that the electrophilic carbon terminus (largest LUMO coefficient) becomes bonded to the more nucleophilic carbon (largest HOMO coefficient). On the other hand the weaker interaction will favor bonding of the more nucleophilic oxygen of the dipole to the site of larger diene LUMO coefficient. This interaction favors the opposite regioselectivity with furan and cyclopentadiene. This mitigates somewhat the effect of the stronger interaction whereas with dihydrofuran a reinforcement of the regioselectivity occurs. The lesser regioselectivity of mesitonitrile oxide cycloadditions to furan as compared to the reactions of benzonitrile oxide may be due to the lower IP and EA of the former nitrile oxide. This will increase the nitrile oxide HOMO interaction somewhat at the expense of the LUMO interaction.

The FMO treatment does not explain the remarkably lower dipolarophilic reactivity of furan in comparison with cyclopentadiene, which must be attributed to the aromatic structure of the former dipolarophile.[6b] From the competition data the increase of the barrier leading to the major cycloadduct could be estimated at 4.0 kcal/mol. This value is compatible with an early transition state for the cycloaddition of nitrile oxides, as suggested by recent ab initio calculations.[26]

With 2-methylfuran only cycloaddition to the unsubstituted double bond, leading to **25**, was observed. The smaller reactivity of the substituted double bond can be ascribed to the destabilizing interaction between the methyl substituent and the nitrile oxide carbon. The shape of the HOMO of 2-meth-

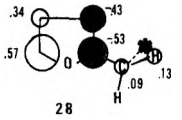
Table II. Eigenvectors and Eigenvalues of the Frontier Orbitals[a]



	HOMO				LUMO			
	C_1	C_2	C_3	E, eV	C_1	C_2	C_3	E, eV
EH[b]								
Cyclopentadiene	0.0	0.5545	0.3767	−12.271	−0.0472 (−0.2256)[c]	0.6447	−0.4359	−8.801
Furan	0.0	0.5655	0.3762	−12.059	−0.3605	0.6708	−0.4022	−8.401
Dihydrofuran	−0.2689	0.5815	0.6194	−12.561	−0.1918	0.8468	−0.8010	−7.708
CNDO/2[d]								
Cyclopentadiene	0.0	0.5746	0.4128	−12.457	0.1261 (−0.2952)[c]	0.5017	−0.3922	3.150
Furan	0.000	0.5866	0.3947	−12.187	−0.3596	0.5586	−0.3508	4.130
Dihydrofuran	−0.5412	0.4205	0.5147	−12.160	−0.1414	0.6805	−0.5979	4.919
MINDO/2[e]								
Cyclopentadiene	0.0	0.5685	0.4211	− 9.038	−0.0056 (−0.1851)[c]	0.5501	−0.4046	0.702
Furan	0.0	0.5756	0.4103	− 8.929	−0.3454	0.5687	−0.3413	0.936
Dihydrofuran	−0.5028	0.4555	0.5903	− 9.039	−0.1645	0.7182	−0.6479	1.259

[a] Experimental geometries were used for the calculations. Furan: B. Bak, D. Christensen, W. B. Dixon, L. Hansen-Nygaard, J. R. Andersen, and M. Schottlander, *J. Mol. Spectrosc.*, **9**, 124 (1962). Cyclopentadiene: L. H. Scharpen and V. W. Laurie *J. Chem. Phys.*, 43, 2765 (1965). 2,3 Dihydrofuran: T. Ueda and T. Shimanouchi, *J. Chem. Phys.*, 47, 5018 (1967). [b] See ref 21. [c] Coefficient of the hydrogen of the CH_2 group above the molecular plane. The hydrogen under the molecular plane (not shown) as opposite sign. [d] J. A. Pople and J. L. Beveridge, "Approximate Molecular Orbital Theory", McGraw-Hill, New York, N. Y., 1970. [e] N. Bodor, M. J. S. Dewar, E. Haselbach, and A. Harget, *J. Am. Chem. Soc.*, **92**, 3854 (1970).

ylfuran, calculated by EH, is given below and results from the mixing of the π orbitals of furan caused by the asymmetric



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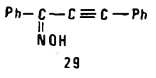
methyl perturbation.[24] Steric effects (or the closed shell repulsion term of the complete perturbation treatment[27]) work in the same direction favoring **25.**

Oxime **3** was obtained in a 1% yield. The free-energy barrier leading to **3** can be calculated to lie 2.6 kcal/mol above the barrier leading to the predominant cycloadduct **1.** Phenylacetylene is also known to react with BNO to yield a mixture of 3,5-diphenylisoxazole and the acetylenic oxime **29** in a ratio



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of 88:12.[28] For the phenylacetylene reaction, the influence of substituents and solvents and the absence of any significant isotope effect[29] support the occurrence of two independent pathways, a concerted cycloaddition and a competing two-step 1,3 addition through a rate-determining electrophilic attack of nitrile oxide on the π system of the aryl acetylene.[30]

A reasonable rationalization of the appearance of the oxime **3** in the reaction mixture of BNO with furan is based on the fact that the cycloaddition is slowed down owing to the loss of aromaticity. Thus the formation of oxime may merely indicate that the concerted pathway has been destabilized to such an extent that a stepwise mechanism, leading to cycloadduct or oxime, may now have a similar activation energy. On the other hand the appearance of oxime may indicate that the stepwise mechanism with furan has some special stabilizing features that are absent in other cases. The approach of the reagents with alignment which would lead directly to the intermediate **27,** from which oxime **3** may be formed, appears indeed to be well stabilized by secondary orbital interactions. The dominant HOMO (furan)–LUMO (BNO) interaction is considerably strengthened whereas an approximate cancellation of secondary orbital effects occurs in the less important LUMO (furan)–HOMO (BNO) interaction. An even better stabilization may be achieved in the case of phenylacetylene by both of the HOMO–LUMO secondary orbital interactions.[31] The relevant secondary interactions are indicated by the dashed lines in the two-plane transition state complexes of Figure 3. A considerable stabilization of the transition state for this alignment, and of the resulting intermediate, should result.

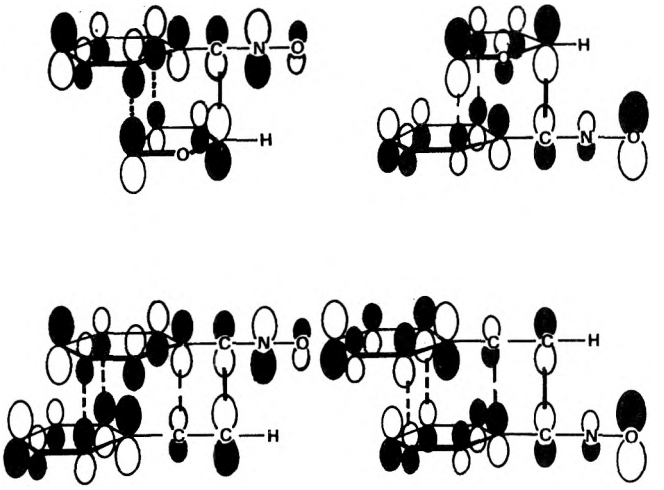


Figure 3. HOMO–LUMO interactions for two-planes transition state complexes. The HOMO and the LUMO of the reactants are represented in the lower and upper part of each complex, respectively. The lobes represent the magnitudes of the atomic orbital coefficient calculated by CNDO/2.

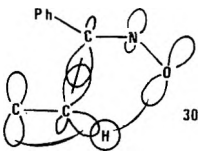
The lack of isotope effect and of rate dependence on the concentration of the base in the phenylacetylene reaction suggested that the proton transfer to form the oxime occurs in a subsequent fast intramolecular process. This is in line with the acid-strengthening effect of adjacent cationic moieties and the suitable location of the oxygen nucleophile for an intramolecular proton transfer. With furan, the additional gain of aromaticity may make this process even easier.

The cycloaddition leading to 3,5-diphenylisoxazole is slow, because of the two large HOMO–LUMO separations.[6b] Alkynes are well known to react slower than alkenes by a power of 10.[32] As a matter of fact, in both these cases where acyclic adducts were detected in the reaction mixtures, furan and phenylacetylene have reduced 1,3-dipolar reactivity toward BNO and also possess the better available geometry for maximal stabilizing interactions in the alignment for a two-step 1,3-addition reaction. Secondary orbital interactions allowed the rationalization of the exo–endo[33] and of the syn–anti[34] specificity in cycloadditions. They form the basis of the concept of steric attraction[35] and—under the heading of nonbonded interactions—were proven to be important contributors to the conformational[36] or configurational[37] preferences of normal molecules as well as of carbonium ions.[38] In the present case, they may be of importance in facilitating an otherwise noncompetitive reaction.

Alternatively viewed, two trajectories appear feasible for overcoming the hill to the products, and frontier molecular orbital theory helps in deciding upon the best ones. Trajectory considerations have been required for the interpretation of the chemistry of trimethylene[39] and tetramethylene[40] intermediates and were recently implicitly proposed for the loss of stereochemistry in the reaction of heterodienes with enol ethers.[41]

Conclusions

A common intermediate does not appear to be required to explain the competing reactions discussed in this paper. Moreover, we have retained the term intermediate in the discussion of the path leading to the oximes only for sake of simplicity. There are no stringent reasons requiring any discrete intermediate other than plausibility even in this case. The whole path leading to oxime could be indeed described as an energetically[42] concerted $[_{\pi}2_a + {}_{\pi}4_s + {}_{\sigma}2_s]$ allowed cycloaddition. As the reagents approach each other, stretching of the bonds and bending of the angles occur, and the allowed path is clearly recognizable in a rather advanced stage of the reaction as shown below.



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As a consequence, in the energy profile of the reaction, the convenient energy minimum of the intermediate—which occurs after that of the transition state has been passed as discussed above—may disappear. Similar flat surfaces and the absence of energy minima have been described for trimethylene and tetramethylene diradicals.[39,40]

Only a detailed analysis of the surface, however, can give insights into the presence or absence of secondary minima on the cycloaddition and 1,3-addition pathways as well as into the availability of low-energy paths connecting them.

At the present, insights for prediction purposes and for devising further experimental tests seem to be attainable by a comparison of the factors affecting the cycloaddition with respect to those ways. Some useful generalizations will be reported elsewhere.

Experimental Section

All melting points are uncorrected. Ir spectra were taken on a Perkin-Elmer Model 257 spectrophotometer as Nujol mulls. NMR spectra were taken in $CDCl_3$ solution, with Me_4Si as internal standard, on a Perkin-Elmer R12 spectrometer (60 MHz). Gas chromatographic analyses were carried out on a glass column, 1% Carbowax 20M and 1% Apiezon L on Gas-Chrom P, with a column temperature of 175 °C on a Carlo Erba Fractovap instrument. Microanalyses were performed by Dr. L. Maggi Dacrema. Satisfactory analytical data (±0.4% for C, N, H) were obtained for all the compounds listed in Table I. Column chromatography and TLC were performed with silica gel H and GF_{254} (Merck), respectively, eluent cyclohexane–EtOAc (9:1 to 7:3) unless otherwise specified. The identification of samples from different experiments was secured by mixture melting points and superimposable ir spectra.

General Procedure for BNO Cycloadditions. To a stirred and ice-cooled solution of benzhydroximic acid chloride (155.5 mg, 1 mmol) and dipolarophile in anhydrous ether (25 ml), a stoichiometric amount of triethylamine (101.9 mg, 0.142 ml) in ether (5 ml) was added over a 30-min period. The mixture was stirred overnight at 0 °C and then kept for 2 days at 25 °C. The triethylamine hydrochloride was filtered off, and the filtrate was evaporated under reduced pressure, leaving a residue. In some cases, on dissolving the triethylamine hydrochloride in water (5 ml), insoluble products were obtained and were added to the residue. Separations were achieved by column chromatography. In all the reactions reported here, 3,4-diphenylfuroxan and 3,5-diphenyl-1,2,4-oxadiazole were eluted first, followed by the cycloaddition products.

Cycloaddition of BNO to Furan. A. To a stirred and ice-cooled solution of benzhydroximic acid chloride (5 g, 32 mmol) in freshly distilled furan (50 ml) a stoichiometric amount (32 mmol) of triethylamine was added over a 2-h period. After the mixture was kept overnight at 0 °C and 2 days at 25 °C, the mixture was diluted with anhydrous benzene (200 ml), the triethylamine hydrochloride was filtered off, and the filtrate was evaporated under reduced pressure, leaving a residue. Column chromatography gave 3,4-diphenylfuroxan (30%) and 3,5-diphenyl-1,2,4-oxadiazole (10%) along with the following products. (1) Mono adduct **1** (730 mg, 12.2%), which was purified by vacuum distillation [bp 170–180 °C (bath)(0.3 mm)]. Crystallization from petroleum ether gave an analytical sample, mp 45–46 °C. (2) Tris adduct **8** (56 mg, 1.2%). The analytical sample, recrystallized from EtOH, had mp 162–316 °C dec. (3) A mixture of mono adduct **2** (17 mg, 0.3%) and bis adduct **5** (738 mg, 15%). The last was separated from the more soluble **2** by crystallization from EtOH. Recrystallization from EtOH gave an analytical sample of **5**, mp 192 °C. From the mother liquors, **2** was isolated by vacuum distillation [bp 170–180 °C (bath)(0.3 mm)]. The analytical sample of **2**, recrystallized from petroleum ether, had mp 70 ° C. Separation could also be achieved using column chromatography, with benzene as eluent. With benzene, **2** is eluted faster than **5**. (4) Oxime **3** (10 mg, 0.2%), mp 149 °C from EtOH, was found to be identical with a sample prepared according to the literature.[14] (5) Bis adduct **7** (30 mg, 0.6%), analytical sample mp 172–173 °C from EtOH. (6) Tris adduct **10** (25 mg, 0.5%), analytical sample mp 161–162 °C dec from EtOH. (7) Lactone **13** (26 mg, 0.5%), analytical sample mp 152–153 °C dec from EtOH, $\nu_{C=O}$ 1782 cm^{-1}. (8) Bis adduct **6** (111 mg, 2.3%), analytical sample mp 227–228 °C from EtOH. (9) Lactone **12** (73 mg 1.1%), analytical sample mp 116–117 °C from EtOH, $\nu_{C=O}$ 1793 cm^{-1}. Similar yields were obtained in duplicate experiments. Eluting with benzene, then benzene/EtOAc, the order of elution of the products is the same, except that **2** is eluted together with **1**, and a better separation of **6** and **12** could be achieved.

B. To a stirred solution of benzhydroximic acid chloride (1 mmol) in furan (100 ml), at room temperature (25 °C), 2 equiv of triethylamine was added. After standing for 3 days, the triethylamine hydrochloride was filtered off and washed with anhydrous benzene. The filtrate was evaporated under reduced pressure, leaving an oily residue. The yields of **1** + **2** (91 ± 1% in a 97:3 ± 0.5% ratio) and **3** (1.0 ± 0.5%) were determined by GLC, by adding as an internal standard a known amount of the BNO adduct with cyclopentene. The area ratio was corrected by using response factors, determined on known mixtures of the adducts and the standard. The pure adducts **1–3** gave well-separated single peaks and are not interconverted under the gas chromatographic conditions. Samples of **1** and **3**, kept for 3 days under the same conditions of the cycloaddition reaction (in furan in the presence of NEt_3/NEt_3·HCl), did not reveal any appreciable interconversion.

The relative addition constants of furan, cyclopentene, and cyclopentadiene were evaluated by the competition method.[43]

Benzhydroximic acid chloride (1 mmol) and cyclopentene 2–2.5 mmol) in furan (50 ml) were reacted as above. By adding a standard, the yields of **1** and of the cyclopentene adduct were determined by GLC. After correction for **2** and **3**, a reactivity ratio of 460 ± 30 of cyclopentene and furan was calculated, as an average on three different reaction mixtures. Similarly, cyclopentadiene was found 2.02 times more reactive than cyclopentene in ether. This corresponds to a decrease of 0.93×10^3 in the reactivity of furan with respect to cyclopentadiene.

Cleavage of 1. A solution of **1** (1 mmol) in HOAc (3 ml) and 20% sulfuric acid (3 ml) was refluxed for 24 h. After cooling, the mixture was poured on ice (20 g) and extracted with ether. The extracts were washed with 10% NaOH, dried on Na_2SO_4, and distilled, giving a 72% yield of 2-benzolyfuran, bp 170 °C, identical (ir, NMR) with a sample prepared according to the literature.[44]

Hydrogenation of 2. **2** (0.2 mmol) and 10 mg of 10% Pd/C in 10 ml of 1:4 HOAc/AcOEt absorbed 1 equiv of hydrogen in 5 min. The catalyst was filtered off, and the filtrate was evaporated under reduced pressure. Crystallization from petroleum ether afforded **14** (60%), mp 77 °C, identical with a sample prepared according to the literature.[13]

Hydration of 1. **1** (5 mmol) was dissolved in $CHCl_3$ (50 ml). On TLC the spot of **1** disappeared in 1 week. After evaporation of the $CHCl_3$, column chromatography yielded the following. (1) Colorless crystals (118 mg, 12%), mp 172–173 °C from EtOH. Anal. Calcd for $C_{22}H_{20}N_2O_5$: C, 67.33; H, 5.14; N, 7.14. Found: C, 67.39; H, 5.29; N, 7.06. NMR: 2.46 m (4 H), 5.33 q (J = 7.3, 5.3 Hz, 2 H), 5.62 q (J = 4.7, 3.3 Hz, 2 H), 5.79 d (J = 7.3 Hz, 2 H), 7.2–8 m (10 H). (2) Colorless crystals (65 mg, 7%), mp 194–195 °C from EtOH. Anal. Calcd for $C_{22}H_{20}N_2O_5$: C, 67.33; H, 5.14; N, 7.14. Found: C, 67.00; H, 5.18; N, 7.31. NMR: 2.43 m (4 H), 5.2–5.5 m (4 H), 5.90 d (J = 7.3 Hz, 2 H), 7.2–8 (10 H). (3) Colorless crystals (405 mg, 41%), mp 145–146 °C from EtOH. Anal. Calcd for $C_{22}H_{20}N_2O_5$: C, 67.33; H, 5.14; N, 7.14. Found: C, 67.47; H, 5.38; N, 6.95. NMR: 1.6–2.1 m (3 H), 2.23–2.5 m (1 H), 5–5.35 m (3 H), 5.6–5.8 m (1 H), 5.66 d (J = 7.3 Hz, 1 H), 5.87 d (J = 7.3 Hz, 1 H), 7.30–7.9 m (10 H). (4) Colorless crystals (130 mg, 13%), mp 172–174 °C from EtOH. Anal. Calcd for $C_{22}H_{20}N_2O_5$: C, 67.33; H, 5.14; N, 7.14. Found: C, 67.73; H, 5.31; N, 7.33. NMR: 2.2–2.5 m (4 H), 4.95–5.15 m (2 H), 5.20–5.35 m (2 H), 5.49 bd (J = 4.7 Hz, 1 H), 5.85 d (J = 7.3 Hz, 1 H), 7.3–8.5 m (10 H). (5) **15** (130 mg, 13%). Recrystallization from benzene gave an analytical sample, mp 126–127 °C, ν_{OH} 3445 cm^{-1}. **15** was acetylated with pyridine/Ac_2O, yielding the acetyl derivatives **16a** (46%) and **16b** (28%) which were separated by column chromatography, eluent benzene/AcOEt 9:1. Recrystallization from hexane gave the analytical samples of **16a**, mp 90–91 °C, $\nu_{C=O}$ 1743 cm^{-1}, and **16b**, mp 93–94 °C, $\nu_{C=O}$ 1743 cm^{-1}.

Cleavage of Bis Adducts 5 and 6. To a stirred suspension of 1 mmol of **5** in 10 ml of Ac_2O, 0.5 ml of boron trifluoride etherate was added. After 1 h, the clear solution was poured onto ice (50 g), stirred for 1 h, and extracted with ether. The extracts were washed successively with 5% $NaHCO_3$ and water and then were dried over Na_2SO_4 and evaporated. The residue was recrystallized from MeOH yielding 268 mg (77%) of ester **20a**. The analytical sample had mp 125 °C, $\nu_{C=O}$ 1760 cm^{-1}. Similarly **6** yielded **20a** in a 61% yield.

A solution of 5 mmol of **20a** in MeOH (30 ml) and concentrated HCl (8 ml) was refluxed for 4 h. After evaporation of the solvent, crystallization of the residue from MeOH afforded 1.0 g (63%) of **20b**, analytical sample mp 162.5–163 °C, ν_{OH} 3330 cm^{-1}. Acetylation of **20b** with Ac_2O (24 h at room temperature) gave back **20a** quantitatively.

A mixture of **20b** (2 mmol) and 2 g of finely powdered $KHSO_4$ was maintained for 4 h at 170 °C. The residue was washed with water and recrystallized from MeOH, yielding 350 mg (60%) of **21**, mp 99 °C, identical with an authentic specimen.[18]

Thermolysis of Tris Adduct 8. **8** (300 mg, 0.70 mmol) was kept at 170 °C for 5 min. Column chromatography yielded 122 mg (80%) of 3,5-diphenyl-1,2,4-oxadiazole and 99 mg (70%) of ketone **11**. Crystallization from hexane gave an analytical sample, mp 89–90 °C $\nu_{C=O}$ 1768 cm^{-1}. The tosylhydrazone of **11** was prepared in a 60%yield by refluxing 73 mg of **11** and an equimolecular amount of tosylhydrazine in 5 ml of MeOH for 15 min. Recrystallization from MeOH gave colorless needles, mp 205–206 °C. Anal. Calcd for $C_{18}H_{17}N_3SO_4$: C, 58.18; H, 4.62; N, 11.32. Found: C, 58.26; H, 4.71; N, 11.30.

Hydrolysis of Lactone 12. **12** (0.5 mmol) was refluxed with 50% H_2SO_4 for 2 h. After dilution with water (40 ml) the mixture was extracted with $CHCl_3$. The extracts were dried on Na_2SO_4 and evaporated, leaving 80 mg (80%) of 3-phenyl-5-isoxazolylacetic acid, mp 124–125 °C from C_6H_6, identical with a sample prepared according to the literature.[20]

Cycloaddition of BNO to Mono Adducts 1 and 2. **1** (500 mg, 2.65 mmol) and 8 mmol of BNO yielded the following products after column chromatography: (1) 35 mg (3%) of tris adduct **8**, (2) 315 mg (32%) of bis adduct **5**, (3) 25 mg (3%) of lactone **13**, (4) 25 mg (3%) of bis adduct **6**, (5) 20 mg (4%) of lactone **12**.

similarly from 75 mg (0.40 mmol) of **2** and 1.2 mmol of BNO, 60 mg (49%) of **7** was obtained.

Cycloaddition of BNO to Bis Adducts 5 and 6. **5** (3.06 g, 10 mmol) and 60 mmol of BNO in anhydrous benzene (200 ml) at room temperature yielded after column chromatography (1) 860 mg (20%) of trisadduct **8**, (2) 680 mg (21%) of lactone **13**, (3) 440 mg (21%) of lactone **12**. Under these conditions, 23% of bis adduct **5** was recovered unchanged.

Similarly, from 153 mg (0.5 mmol) of **6** and 3 mmol of BNO, 36 mg (15%) of tris adduct **10** and 19 mg (12%) of lactone **13** were obtained. Unchanged **6** (58 mg, 38%) was recovered.

Cycloaddition of BNO to Lactone 12. From 0.5 mmol of **12** and 3 mmol of BNO, 100 mg (62%) of lactone **13** and 20 mg (20%) of unchanged **12** were recovered by column chromatography.

Cycloaddition of *p*- and *m*-Nitrobenzonitrile Oxide to Furan. *p*-Nitrobenzhydroximic acid chloride (25 mmol) in 100 ml of furan yielded, after the usual workup, 3.5 g (60%) of mono adduct as pale yellow crystals, mp 145–145 °C from MeOH. Anal. Calcd for $C_{11}H_8N_2O_4$: C, 56.90; H, 3.47; N, 12.07. Found: C, 56.78; H, 3.53; N, 11.99. Cleavage of 3 mmol of the adduct by refluxing with 1:1 $HOAc/H_2SO_4$ (20%) for 24 h yielded 400 mg (61%) of 2-*p*-nitrobenzoylfuran, pale yellow crystals, mp 184 °C from MeOH, $\nu_{C=O}$ 1640 cm^{-1}. Anal. Calcd for $C_{11}H_7NO_4$: C, 60.83; H, 3.25; N, 6.45. Found: C, 60.73; H, 3.49; N, 6.64. A solution of 2-*p*-nitrobenzoylfuran (2 g) in EtOH (150 ml) absorbed 3 equiv of hydrogen in 1 h in the presence of 10% Pd/C (0.2 g). After filtration of the catalyst and evaporation of the solvent, the crude 2-*p*-aminobenzoylfuran (1.7 g) was dissolved in 5% HCl (25 ml), $NaNO_2$ (0.67 g) was added, and the mixture was refluxed for 2 h. Extraction with ether gave 0.6 g (34%) of 2-*p*-hydroxybenzoylfuran, mp 163–164 °C from water, identicl with a sample prepared according to the literature.[45]

Similarily, 25 mmol of *m*-nitrobenzhydroximic acid chloride yielded 2.0 g (34%) of mono adduct, pale yellow crystals, mp 113 °C from MeOH. Anal. Calcd for $C_{11}H_8N_2O_4$: C, 56.90; H, 3.47; N, 12.07. Found: C, 56.69; H, 3.53; N, 12.03. Hydrolysis as above yielded 2-*m*-nitrobenzoylfuran, pale yellow crystals, mp 124.5 °C from MeOH, $\nu_{C=O}$ 1640 cm^{-1}. Anal. Calcd for $C_{11}H_7NO_4$: C, 60.83; H, 3.25; N, 6.45. Found: C, 60.99; H, 3.36; N, 6.82.

Cycloaddition of Mesitonitrile Oxide with Furan. A solution of 4 g (24.8 mmol) of mesitonitrile oxide in 70 ml of furan was kept at room temperature for 8 months. Bis adduct **23** (1.15 g) crystallized out. Recrystallization from EtOH gave an analytical sample, mp 257–258 °C. The filtrate was evaporated. Crystallization from ethanol yielded a mixture of 0.8 g of **23** (combined yield 40%) and 0.29 g (6%) of bis adduct **24**, which was separated by column chromatography, with benzene as eluent. An analytical sample of **24** was obtained by crystallization from EtOH and had mp 264–266 °C dec. The mother liquors were evaporated and distilled, yielding 1.6 (28%) of mono adduct **22**, bp 160–180 °C (bath) (0.1 mm), analytical sample mp 91 °C from petroleum ether.

Cycloaddition of BNO to 2-Methylfuran. Benzhydroximic acid chloride (5 g, 32 mmol) in 50 ml of 2-methylfuran yielded 1.77 g ((28%) of **25** and 0.17 g (3%) of bis adduct **26**. The analytical sample of **25** and **26** had mp 70 °C (from petroleum ether) and 213 °C (from EtOH), respectively.

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Registry No.—**1**, 59728-61-9; **2**, 59728-62-0; **5**, 59752-62-4; **6**, 59752-63-5; **7**, 59728-63-1; **8**, 59728-64-2; **10**, 59728-65-3; **11**, 59728-66-4; **11** tosylhydrazone, 59728-67-5; **12**, 59728-68-6; **13**, 59728-69-7; **15a**, 58728-70-0; **15b**, 59752-64-6; **16a**, 59728-71-1; **16b**, 59752-65-7; **17** isomer A, 59728-72-2; **17** isomer B, 59752-66-8; **18** isomer A, 59752-67-9; **18** isomer B, 59752-68-0; **19** isomer A, 59752-69-1; **19** isomer B, 59752-70-4; **20a**, 59728-73-3; **20b**, 59728-74-4; **22**, 59728-75-5; **23**, 59728-76-6; **24**, 59728-77-7; **25**, 59728-78-8; **26**, 59728-79-9; benzhydroximic acid chloride, 698-16-8; BNO, 873-67-6; furan, 110-00-9; *p*-nitrobenzhydroximic acid chloride, 1011-84-3; monoadduct A, 59728-80-2; 2-*p*-nitrobenzoylfuran, 21494-08-6; *m*-nitrobenzhydroximic acid chloride, 33512-94-6; monoadduct B, 59728-81-3; 2-*m*-nitrobenzoylfuran, 59728-82-4; mesitonitrile oxide, 59728-83-5; 2-methylfuran, 534-22-5.

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Reactions of 3-Methylbenzyne with 2-Substituted Furans.[1] Steric Effects

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3-Methylbenzyne generated from two pairs of isomeric precursors, namely, 2-amino-3-methylbenzoic acid (**1**)–2-amino-6-methylbenzoic acid (**2**) and 2-fluoro-3-methylbromobenzene (**3**)–6-fluoro-2-methylbromobenzene (**4**), has been reacted with 2-methylfuran (**5**), 2-*tert*-butylfuran (**6**), 2-(1,3-dioxolan-2-yl)furan (**7**), and 2-carbomethoxyfuran (**8**). The proportions of isomeric adducts produced were the same (±2%) for each furan and are expressed as ratio of less hindered isomer (1,5-naphthalene derivative) to more hindered isomer (1,8-naphthalene derivative) as follows: for **5**, 58/42; **6**, 64/36; **7**, 61/39; **8**, 57/43. Thus the addition of an unsymmetrical benzyne to a furan seems very slightly affected by steric or polar effects. The results are interpreted as evidence supporting a true benzyne intermediate.

Benzyne reacts readily with furans to form 1,4-dihydro-1,4-epoxynaphthalenes which are of great synthetic interest because of their ready conversion to other types of compounds.[3,4] In order to increase the synthetic utility and understanding of this type of reaction, we have studied the reactions of 3-methylbenzyne prepared from two isomeric pairs of precursors with 2-substituted furans.

Although a fair amount of work has been done on the relative reactivities in Diels–Alder type reactions of benzynes (prepared from different precursors) with pairs of other reactants,[5,6] little is known about steric effects.[7] Conflicting steric results have been reported in the reaction of 3,5-di-*tert*-butylfuran[8] (in which the predominant adduct proved to be the more hindered 1,3,6,8-tetra-*tert*-butyl-1,4-dihydro-1,4-epoxynaphthalene) and with 2-benzyl-5-*tert*-butylfuran[9] (in which the ratio of the less hindered isomer to the more hindered isomer was 14/11).

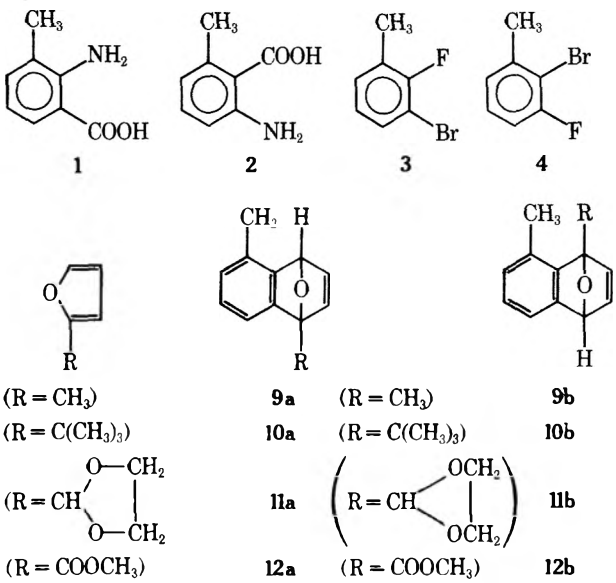
In the work reported herein we have determined the products formed when two pairs of isomeric compounds, 2-amino-3-methylbenzoic acid (**1**)–2-amino-6-methylbenzoic acid (**2**) and 2-fluoro-3-methylbromobenzene (**3**)–6-fluoro-2-methylbromobenzene (**4**), were treated to produce 3-methylbenzyne in the presence of 2-methylfuran (**5**), 2-*tert*-butylfuran (**6**), 2-(1,3-dioxolan-2-yl)furan (**7**), and 2-carbomethoxyfuran (**8**), to yield the isomeric adduct pairs (**9a, 9b**), (**10a, 10b**), (**11a, 11b**), and (**12a, 12b**). The results are summarized in Table I.

Examination of the results in Table I reveals that the ratio of products obtained from isomeric 3-methylbenzyne precursors is the same, within experimental error, for each of the

Table I. Reactions of Isomeric 3-Methylbenzyne Precursors with 2-Substituted Furans[a]

Benzyne precursor	Yield, %,[b,c] and ratio[d] of adducts for R = CH_3 9a/9b	$C(CH_3)_3$ 10a/10b	 11a/11b	$COOCH_3$ 12a/12b
1[e]	(50)[b] 58/42	(51)[b] 64/36	(81)[b] 61/39	(82)[c] 57/43
1[f]	(70)[b] 58/42	(59)[b] 65/35	(50)[b] 59/41	(54)[b] 57/43
2[e]	(44)[b] 58/42	(53)[b] 62/38	(75)[c] 61/39	(75)[c] 58/42
3[g]	(74)[b] 58/42	(73)[b] 64/36	(81)[c] 61/39	*h*
4[g]	(76)[b] 58/42	(74)[b] 62/38	(76)[c] 61/39	*h*

[a] In all experiments the quantity of THF was the same and the ratio of benzyne precursor to furan was one. [b] Isolated yield of mixture of adducts; see Experimental Section. [c] Yield estimated after column chromatography of reaction mixture; see Experimental Section. [d] Ratios reported represent the average of a number of runs in which the results generally checked to within ±1% of the average. [e] Diazotization and decomposition as described.[10] [f] Diazotization and decomposition as described.[11] [g] Pure sublimed magnesium was used under conditions similar to those described.[4,12] [h] Reaction not carried out.



substituted furans studied. These facts support the concept that 3-methylbenzyne is the true reactant and not some partly reacted intermediate. Thus the results of the present work support the ideas of Huisgen and co-workers,[6] who studied the competitive reactions of symmetrical benzyne with different benzyneophiles. In addition our studies indicate that there is very little effect of a polar or steric nature in the Diels–Alder type reactions involved.

Experimental Section[13]

2-Amino-3-methylbenzoic Acid (1). In a 4-l. beaker equipped with a mechanical stirrer and thermometer were placed 90 g (0.54 mol) of chloral hydrate, 453 g of Na_2SO_4, and 1.5 l. of water. A solution of 51.5 g (0.48 mol) of freshly distilled *o*-toluidine and 410 g (2.5 mol) of hydroxylamine sulfate in 500 ml of water containing 50 ml of concentrated HCl was added rapidly and the stirred mixture was heated to 45 °C during 1.5 h to 52 °C in 45 min, and then to 65 °C for 1 h. On cooling there was obtained 78.5 g (91.6%) of 2-hydroxyiminoacet-*o*-toluidide, mp 119–120 °C (lit.[14] mp 121 °C, 63%), suitable for the next step after drying in air. To 800 ml of anhydrous HF[15] in a 2-l. polyethylene bottle was added 100 g of the above *o*-toluidide in portions during 45 min. After the HF was allowed to evaporate (2–3 days), the residue was triturated with a solution at 60 °C of 50 ml of H_2SO_4 and 400 ml of water. The crude isatin was collected by filtration of the cooled suspension, washed with water, and dissolved in 700 ml of hot 5% NaOH. After filtration through Celite (filter aid, J. T. Baker Chemical Co.) the filtrate was acidified with concentrated HCl to yield 93.7 g (100%) of orange-red 7-methylisatin, mp 270–271 °C (lit.[16] mp 266 °C). To a solution of 80.0 g of 7-methylisatin in 20 g of NaOH, 80 g of KCl, and 900 ml of water at 8–10 °C was added 88 g of cooled 30% H_2O_2 during 1.5 h. After an additional 45 min at 20 °C, the addition of 180 ml of acetic acid caused precipitation of an almost colorless solid, **1**, mp 166–168 °C, in almost quantitative yield. Pure **1**, mp 174–176 °C (lit.[17] mp 172 °C), was obtained in 83% yield by recrystallization from water. Only pure **1** was used in the generation of 3-methylbenzyne.

2-Amino-6-methylbenzoic Acid (2). The nitration of acet-*o*-toluidide was carried out as described[18] on a 2-mol scale. The alkaline method of separation (ref 18, footnote 8) was used to obtain 237 g (61% based on *o*-toluidine) of 2-methyl-6-nitroacetanilide, mp 155–157 °C, which was then hydrolyzed almost quantitatively to 2-methyl-6-nitroaniline, mp 92–94 °C, essentially as described.[17] This amine (47.3 g) was converted into 42.7 g (83%) of 2-methyl-6-nitrobenzonitrile, mp 107–108 °C (lit.[19] mp 109–110 °C, 63%) as described.[17] Hydrolysis to recrystallized 2-methyl-6-nitrobenzamide, mp 158–159 °C (lit.[17] mp 158 °C, 71%) in 72% yield was accomplished by heating the nitrile (83.7 g) with a solution of 330 ml of concentrated H_2SO_4 and 175 ml of water at 110–115 °C for 1 h. The amide in the sulfuric acid filtrate was diazotized with sodium nitrite to yield 21 g (22%) of 2-methyl-6-nitrobenzoic acid, mp 151–153 °C. Diazotization of the solid amide[17] yielded additional acid, mp 151–153 °C, the overall yield from nitrile being 76%. Reduction to 2-amino-6-methylbenzoic acid (**2**), mp 125–126 °C (lit.[17] mp 125–126 °C), was accomplished by treating a hot solution of 69.0 g of 2-methyl-6-nitrobenzoic acid in 80 ml of 29% ammonia with a suspension of 680 g of $FeSO_4$ in 2 l. of ammonium hydroxide. After heating for several hours to allow ammonia to escape the mixture was acidified with acetic acid to yield 33.0 g (57%) of **2**.

3-Bromo-2-fluorotoluene* (3). Nitration of *m*-toluic acid to 2-nitro-3-methylbenzoic acid, mp 218–220 °C, was accomplished in 50% yield as described.[19] To a stirred suspension of 107.0 g of the nitro acid in 900 ml of concentrated H_2SO_4 at −5 to 0 °C was added 42.2 g of sodium azide. The suspension became blue violet. On warming toward 60 °C (final temperature) the color changed to pink, gas evolution occurred continuously, and a clear solution was obtained. This was poured on ice and the mixture was made alkaline with ammonium hydroxide. The crude solid was collected and recrystallized from benzene–cyclohexane to yield 74.4 g (83%) of orange-yellow 2-nitro-3-methylaniline, mp 104–106 °C (lit.[20] mp 108 °C). This amine was converted into 3-bromo-2-nitrotoluene, bp 152–156 °C (35 mm), pure by GLC, in 82% yield as described.[20] Reduction to 2-bromo-6-methylaniline, bp 140–144 °C (40 mm), was accomplished in 86% yield as described.[21] Replacement of the amino group by fluorine was accomplished as described[22] to yield GLC pure **3** as a colorless oil, bp 185–186 °C, in 70% yield. Before use in generating 3-methylbenzyne, benzene solutions of **3** and **4** were washed with concentrated H_2SO_4 in the cold until the acid layer was colorless. The halides were then recovered and distilled.

2-Bromo-3-fluorotoluene* (4). A suspension of 100 g of 2-methyl-6-nitroaniline (prepared by nitration of acet-*o*-toluidide as described[18]) in 150 ml of 48% HBr and 200 ml of water was converted[23] into 94 g (60%) of 2-bromo-3-nitrotoluene, bp 166–170 °C (45 mm) [lit.[23] bp 135–136 °C (8 mm)]. Reduction to 2-bromo-3-methylaniline,* bp 145–148 °C (45 mm), was accomplished in 95% yield as described for a similar case.[21] Conversion of this bromo amine into **4**, bp 184–187 °C, was effected in 50% yield essentially as described for a similar case.[22] Pure **4**, bp 187 °C, was obtained by fractionation in a small column.

2-*tert*-Butylfuran (6). A mixture of 37.8 g of methyl 2-furoate and 28.0 g of *tert*-butyl chloride was added dropwise during 40 min to an ice–salt cooled suspension of 60 g of $AlCl_3$ in 300 ml of CS_2. After a

further 3 h at this temperature the mixture was poured on ice. After the usual workup the residue yielded 51.1 g (93.6%) of GLC pure methyl 5-*tert*-butyl-2-furoate, bp 112–114 °C (20 mm).[24] After alkaline hydrolysis there was obtained 47 g of 5-*tert*-butyl-2-furoic acid, mp 98–100 °C (lit.[25] mp 103.5–104.5 °C). After decarboxylation as described[25] there was obtained **6**, bp 119–120 °C, in 51% yield. There was some loss of product in the forerun. The use of an efficient fractionation column is recommended for future work.

2-(1,3-Dioxolan-2-yl)furan (7). This compound, bp 74–76 °C (1 mm), was obtained essentially as described.[26]

Reactions of 3-Methylbenzyne Precursors with Furans. The general procedure (footnote *e*, Table I) adopted for **1** and **2** was as follows. A solution of 3.0 g (0.02 mol) of **1** (or **2**) in 20 ml of THF was added dropwise from a pressure equalizing addition funnel during 2–2.5 h to a stirred solution at 50 °C of 0.02 mol of **5, 6, 7,** or 8 and 3.4 ml (2.96 g, 0.025 mol) of freshly distilled amyl nitrite in 20 ml of THF. After another 1 h the THF was removed under vacuum and the residue was taken up in 200 ml of ether and worked up as usual. The crude product obtained after removal of ether was analyzed (three duplicate injections) by GLC[27] to give the ratios reported in Table I (footnote *d*). The yields of adduct obtained by vacuum distillation of these products are represented by footnote *b* in Table I. In a few cases, footnote c in Table I, the crude products were chromatographed on alumina (treated with ethyl acetate before use) to afford the yields recorded. The ratios, *d*, obtained by this procedure starting from **1** were the same as those obtained when procedure *f*, Table I, was used. Procedure *f* was as follows. To a magnetically stirred solution of 3.0 g of **1** and 150 mg of trichloroacetic acid in 20 ml of THF in a 100-ml beaker cooled with ice water was added 3.2 ml (2.79 g) of freshly distilled amyl nitrite, the temperature rising as high as 20 °C. After stirring for 1–1.5 h, the buff precipitate was collected, washed with THF until the washings were colorless, and used directly while wet with solvent in the reactions with the furans. On an air-dried basis the yields of betaines were 95–99%, but because of danger in handling the dry materials, only solvent-wet products were used. We found it advantageous to use slightly larger amounts of CCl_3COOH than recommended[11] because the yields of adducts with the furans were somewhat higher when betaines thus made were used. The solvent-wet betaines were then added to a solution of 1 equiv of furan in THF and the mixture (total volume 40 ml) was heated at 50 °C until gas evolution was complete (2–3 h). After removal of solvent, isolation and analysis of the adduct mixture were similar to those described above.

The general procedure for generating and reacting **3** and **4** was as follows. In a flamed 100-ml three-necked flask fitted with a reflux condenser, stirrer, and pressure-equalizing dropping funnel were placed 20 ml of THF freshly distilled over $LiAlH_4$, 0.02 mol of substituted furan, and 0.022 g-atom of pure sublimed magnesium.[28] While a slow stream of nitrogen was flowing, a solution of 0.02 mol of freshly distilled bromofluorotoluene, **3** or **4**, in 20 ml of THF was added during 30 min to the contents of the flask held at reflux. After the addition was completed the contents were held at reflux for 2 h, cooled, and treated with 20 ml of saturated NH_4Cl solution. After the usual workup, the solvents were removed and the residue analyzed by GLC.[27] The yields reported in Table I were obtained by distillation of the crude products or by chromatography as indicated by footnotes *b* and *c*, Table I.

***Proof of* Structure, 1,4-Dihydro-1,5-dimethyl-1,4-epoxynaphthalene (9a) and 1,4-Dihydro-1,8-dimethyl-1,4-epoxynaphthalene (9b).** A vacuum distilled sample (0.60 g) of a mixture of **9a** and **9b** (63:37 by GLC analysis, not the same as the 58:42 ratio of total product because of slight fractionation during distillation) was hydrogenated in methanol over 5% Pd/C (50 mg) for 30 min at 45 psi of hydrogen. After removal of the catalyst by filtration and the solvent by distillation the residue was held at reflux for 1 h in ethanol saturated with dry HCl. The aromatized product (500 mg) had two components by GLC (column B, 63:37). The minor component was shown to be 1,8-dimethylnaphthalene by peak enhancement of the minor peak (retention time 2.5 min of column B[13] at 145 °C with synthetic pure 1,8-dimethylnaphthalene.[29] In another experiment similar to the above, chromatography (over silicic acid using 40–50 °C petroleum ether) of the aromatic dimethylnaphthalene fraction followed by recrystallization from methanol of the fraction rich in the major component yielded some pure 1,5-dimethylnaphthalene,[30] mp 78–80 °C, *m/e* 156.[31]

Proof of Structure, 1-*tert*-Butyl-1,4-dihydro-1,4-epoxy-5-methylnaphthalene (10a) and 1-*tert*-Butyl-1,4-dihydro-1,4-epoxy-8-methylnaphthalene (10b). These compounds were obtained by reactions similar to those described above. Analyses as to compounds were made by GLC, column A.[27] The identity of the two components was assigned by NMR analysis. There were two singlets corresponding to $ArCH_3$, a major (2.20 ppm) and a minor (2.41 ppm). In the case of 5,7-di-*tert*-butyl-1,4-dimethylnaphthalene,[8b] the less hindered 1-methyl group resonates at 2.61 ppm and the more hindered 4-methyl group at 2.77 ppm. This fact led us to assign the structure **10a** to the compound whose $ArCH_3$ group was at 2.20 and 10*b* having $ArCH_3$ at 2.41. In keeping with these assignments the $ArCH_3$ in 1-*tert*-butyl-1,4-epoxy-5-methyl-1,2,3,4-tetrahydronaphthalene (obtained by reduction over Pd/C), the major component, resonates at 2.30 ppm while the $ArCH_3$ resonance in the minor component, 1-*tert*-butyl-1,4-epoxy-8-methyl-1,2,3,4-tetrahydronaphthalene, was at 2.50 ppm. Confirmation of the above assignments was obtained by considering the resonances of the hydrogens on the peri positions involving the 1,4-epoxy linkage. In **10a** (the major component), this hydrogen (on C_4) resonated at 5.53 ppm whereas in **10b** the value was 5.36 ppm. In the tetrahydro compounds, obtained by reduction of the mixture of **10a** and **10b** over Pd/C, the corresponding values were 5.26 (multiplet in major component) and 5.13 ppm (*m* in minor). Attempts to aromatize the tetrahydro compound mixture with acid led to mixtures in which some loss of *tert*-butyl groups had occurred.

***Proof of* Structure, 1,4-Dihydro-1-(1,3-dioxolan-2-yl)-1,4-epoxy-5-methylnaphthalene* (11a) and 1,4-Dihydro-1-(1,3-dioxolan-2-yl)-1,4-epoxy-8-methylnaphthalene* (11b).** Mixtures of **11a** and **11b** obtained in the addition reactions were combined and chromatographed over silica gel (100–200 mesh, 100 g/g of mixture) using 20% ethyl acetate in benzene as eluent. The material in the first fraction proved to be the major component and was further recrystallized thrice from ethyl acetate–hexane to fairly pure **11a,** mp 91.0–92.5 °C, *m/e* 230.[31] The analytical sample of **11a,** mp 94.8–95.1 °C, NMR ($CDCl_3$) 2.26 (3, s, $ArCH_3$), 5.56 [1, s, $CH(-O-)_2$], 5.78 ppm (1, s, C_4 H), was obtained by further recrystallization. From the second fraction in a similar way was isolated a small amount of the minor component, **11b** mp 109–110 °C. The analytical sample of **11b,** mp 111.8–112.0 °C, *m/e* 230, NMR ($CDCl_3$) 2.38 (3, s, $ArCH_3$), 5.66 (1, s, C_4 **H**), 5.96 ppm [1, s, $CH(-O-)_2$], was obtained by further recrystallization. The assignment of **11a** and **11b** was made because the hydrogen on the carbon (C_4) in **11a** containing the epoxy link was further downfield (δ 5.78) when sterically hindered by the peri methyl group than in the isomer (δ 5.66) where this hydrogen is next to a peri hydrogen.[8b]

In addition to the NMR evidence, samples of **11a** and **11b** were catalytically reduced (Pd/C) in 80% yields to 1-(1,3-dioxolan-2-yl)-1,4-epoxy-5-methyl-1,2,3,4-tetrahydronaphthalene,* mp 80–81 °C, *m/e* 232, and 1-(1,3-dioxolan-2-yl)-1,4-epoxy-8-methyl-1,2,3,4-tetrahydronaphthalene,* mp 91.5–92.0 °C respectively. The dihydro adduct above, mp 80–81 °C (40 mg), was heated with 2 ml of 98% formic acid on a steam bath for 30 min. The aromatic aldehyde thus obtained was immediately oxidized by heating with aqueous sodium hydroxide and the freshly prepared Ag_2O from 200 mg of $AgNO_3$ to yield 24 mg (67%) of 5-methyl-1-naphthoic acid, mp 184–186 °C (lit.[32] mp 188–189 °C).

The dihydro adduct above, mp 91.5–92.0 °C (250 mg), was similarly heated with 98% formic acid to yield a mixture which was not readily oxidized by Ag_2O. Chromatography afforded 70 mg of 8-methyl-1-naphthaldehyde, mp 65–67 °C, which proved identical with an authentic sample, mp 70–71 °C, prepared as described[33] (lit.[33] mp 71.5–72.0 °C) from 1,8-dimethylnaphthalene, by GLC, TLC, and ir measurements.

Proof of Structure, Methyl 1,4-Dihydro-1,4-epoxy-5-methyl-1-naphthoate* (12a) and Methyl 1,4-Dihydro-1,4-epoxy-8-methyl-1-naphthoate* (12b). About 2 g of a mixture of **12a** and **12b** was subjected to preparative TLC on silica gel. Only one broad band was obtained but this was separated into upper and lower halves. On extraction of the upper half 900 mg of product was obtained. Crystallization from ether–hexane afforded 500 mg of product, mp 95–97 °C, which proved to be **12a.** The analytical sample melted at 96.5–97.0 °C. Similarly from the lower half there was isolated a sample of **12b,** mp 55–56 °C.

On catalytic hydrogenation in methanol over Pd/C, 500 mg of **12a** afforded 420 mg of methyl 1,4-epoxy-5-methyl-1,2,3,4-tetrahydro-1-naphthoate,* mp 69–70 °C, ir (KBr) 1750 cm^{-1}, which, on heating with methanolic HCl for 2 h, afforded methyl 5-methyl-1-naphthoate. Aqueous alkaline hydrolysis afforded 5-methyl-1-naphthoic acid,[32] mp 186–188 °C, identical with the acid formed (see above) by oxidation of 5-methyl-1-naphthaldehyde by melting point and mixture melting point. In a similar way the adduct **12b** was hydrogenated and the crude product aromatized by heating with methanolic HCl to methyl 8-methyl-1-naphthoate, ir (neat) 1725 cm^{-1}. After heating in aqueous methanolic KOH for 16 h, the acid obtained by the usual

method (some ester, ca. 30% still remained) melted at 154.0–154.5 °C (lit.[34] mp 153 °C), ir (KBr) 1688 cm^{-1}, identical by mixture melting point with a sample obtained by oxidation of 8-methyl-1-naphthaldehyde (see above).

Registry No.—**1,** 4389-45-1; **2,** 4389-50-8; **3,** 59907-12-9; **4,** 59907-13-0; **5,** 534-22-5; **6,** 7040-43-9; **7,** 1708-41-4; **8,** 611-13-2; **9a,** 59907-14-1; **9b,** 59907-15-2; **10a,** 59907-16-3; **10b,** 59907-17-4; **11a,** 59907-18-5; **11b,** 59907-19-6; **12a,** 59907-20-9; **12b,** 59907-21-0; o-toluidine, 95-53-4; hydroxylamine sulfate, 13973-61-0; 2-hydroxyiminoacet-o-toluidide, 1132-03-2; 7-methylisatin, 1127-59-9; acet-o-toluidide, 120-66-1; 2-methyl-6-nitroacetanilide, 59907-22-1; 2-methyl-6-nitroaniline, 570-24-1; 2-methyl-6-nitrobenzonitrile, 1885-76-3; 2-methyl-6-nitrobenzamide, 40637-78-3; 2-methyl-6-nitrobenzoic acid, 13506-76-8; *m*-toluic acid, 99-04-7; 2-nitro-3-methylbenzoic acid, 5437-38-7; 2-nitro-3-methylaniline, 601-87-6; 3-bromo-2-nitrotoluene, 52414-97-8; 2-bromo-6-methylaniline, 53848-17-2; 2-bromo-3-nitrotoluene, 41085-43-2; 2-bromo-3-methylaniline, 54879-20-8; *tert*-butyl chloride, 507-20-0; methyl 5-*tert*-butyl-2-furoate, 59907-23-2; 5-*tert*-butyl-2-furoic acid, 56311-39-8; 1-(1,3-dioxolan-2-yl)-1,4-epoxy-5-methyl-1,2,3,4-tetrahydronaphthalene, 59907-24-3; 1-(1,3-dioxolan-2-yl)-1,4-epoxy-8-methyl-1,2,3,4-tetrahydronaphthalene, 59907-25-4; methyl 1,4-epoxy-5-methyl-1,2,3,4-tetrahydro-1-naphthoate, 59907-26-5; methyl 8-methyl-1-naphthoate, 15724-49-9; 8-methyl-1-naphthaldehyde, 6549-57-1.

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(2) Postdoctoral Research Associate.
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The Ortho Effect in the Pyrolysis of Iodonium Halides. A Case for a Sterically Controlled Nucleophilic Aromatic (SN) Substitution Reaction[1]

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A series of arylphenyliodonium chlorides, bromides, and iodides-131 were pyrolyzed and the product compositions determined by GC. In most cases the quantities of the aryl halides obtained were those expected if a nucleophilic aromatic substitution (SN) mechanism were operative. However, in those cases in which an ortho methyl group was present on one of the aryl rings, the anion preferentially attacked that ring, giving product compositions opposite of those expected from nucleophilic aromatic substitution. The presence of a second ortho methyl group increased this effect. Also, pyrolysis of phenyl-2,5-dimethylphenyliodonium halides gave more 2-halo-*p*-xylene than phenyl-2,4-dimethylphenyliodonium halides gave 2-halo-*m*-xylene. These data are best accommodated by a nucleophilic aromatic substitution mechanism in which product formation is sterically controlled when ortho methyl groups are present.

Diaryliodonium halides decompose upon heating to give mixtures of aryl iodides and aryl halides derived from the halide ion of the iodonium salt (eq 1).[3-10]

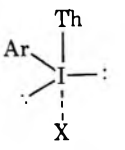
$$\mathrm{ArIAr'\ X^-} \xrightarrow{\text{heat}} \mathrm{ArI + Ar'X + ArX + Ar'I} \qquad (1)$$

For example, phenyl-*p*-anisyliodonium bromide decomposes by two paths, one leading to *p*-bromoanisole and iodobenzene (path I) and the other to *p*-iodoanisole and bromobenzene (path II) (eq 2).[9]

$$p\text{-}\mathrm{CH_3OC_6H_4IPh\ Br^-} \begin{cases} \xrightarrow{\text{path I}} \mathrm{PhI} + p\text{-}\mathrm{CH_3OC_6H_4Br} \\ \qquad\qquad \text{anion-substituted aryl} \\ \xrightarrow{\text{path II}} \mathrm{PhBr} + p\text{-}\mathrm{CH_3OC_6H_4I} \end{cases} \qquad (2)$$

(For the purpose of clarity, in this paper path I will always indicate the mechanism in which the halide ion attacks the *substituted* aryl ring, leading to anion-substituted aryl and iodobenzene.)

Recently, a study of the mechanism of this pyrolysis has been carried out by Yamada and co-workers.[5-7] Substituted phenyl-*p*-tolyliodonium bromides were pyrolyzed and the products were accounted for in terms of a bimolecular nucleophilic aromatic substitution mechanism.[7] Also studied were a number of aryl-2-thienyliodonium chlorides and bromides, and the product compositions suggested that the reaction proceeds by interaction of the thienyl group and the halide ion, the intermediate having a trigonal bipyramidal structure (1).[6] However, when the diaryliodonium bromides



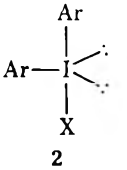
1

Th = thienyl

were substituted with an ortho methyl group, the bromide ion preferentially attacked the aryl group least able to bear the developing negative charge, i.e., the aryl ring containing one or more methyl groups. To account for this effect of the ortho methyl substituents, these workers proposed a mechanism involving a methyl-substituted phenyl cation.[5]

We have observed this ortho effect before in the pyrolysis of sulfonium halides. For example, pyrolysis of phenyl-*p*-tolyl-2,5-dimethylphenylsulfonium bromide at 250 °C afforded bromobenzene, *p*-bromotoluene, and 2-bromo-*p*-xylene in the ratio of 1.9:1.0:11.8, respectively, along with the corresponding diaryl sulfides. As the halide ion was varied from chloride to bromide to iodide the yield of 2-halo-*p*-xylene increased markedly. These results are best accommodated by a mechanism involving nucleophilic attack of halide ion upon the sulfur atom in the sulfonium cation to form a tetracovalent sulfur intermediate, with subsequent SN-like collapse to form products. The increase in yield of the 2-halo-*p*-xylene formed as the size of the halide ion is increased is attributed to increased crowding in the tetracovalent intermediate, the major decomposition pathway of which being that providing maximum relief of steric strain.[11]

The similarities of product compositions obtained from the pyrolyses of the sulfonium and iodonium salts suggested to us that the iodonium halides might be behaving in an analogous manner; namely, nucleophilic attack upon the positive iodine atom in the iodonium cation to form a tricovalent iodine intermediate (2), with subsequent SN-like collapse to form



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products. Accordingly, we have pyrolyzed a series of arylphenyliodonium chlorides, bromides, and iodides-131 in order to test this hypothesis.

Results

Synthesis of Arylphnyliodonium Halides. Substituted arylphenyliodonium halides were prepared in good yield and purity from the appropriate aryliodo diacetate or iodosobenzene and aromatic compound in a solution of acetic anhydride and concentrated sulfuric acid (Table I). When mesitylene and *p*-xylene were employed the position of substitution was unambiguous. Use of *m*-xylene, anisole, and toluene opened up possibilities of isomer formation; in practice, however, exclusive para substitution occurred with toluene and anisole, while *m*-xylene yielded exclusively the phenyl-2,4-dimethylphenyliodonium salt. The iodonium iodides prepared by metathesis were contaminated with iodonium bromide, but the desired degree of purity could be achieved by recrystallization. These observations are in accord with those of Beringer.[4]

Product Compositions. Product compositions for the pyrolysis of the series of iodonium halides are listed in Table II. In iodonium halides which contained a methyl or methoxyl

Table I. Preparation of Diaryliodonium Halides

Starting compd	Registry no.	ArH	Registry no.	Iodonium cation	Anion	Registry no.	Mp, °C	Yield, %
Iodosobenzene	536-80-1	Anisole[a]	100-66-3	Phenyl-*p*-anisyl-	Br^-		176–178[b]	80
Phenyl-*p*-anisyl-iodonium bromide	2665-61-4			Phenyl-*p*-anisyl-[f]	I^-		173–174[c]	65
Iodosobenzene diacetate	3240-34-4	Toluene	108-88-3	Phenyl-*p*-tolyl-	Br^-		169–170[d]	57
Iodosobenzene diacetate	3240-34-4	Toluene	108-88-3	Phenyl-*p*-tolyl-	Cl^-	56530-34-8	197–199	53
Phenyl-*p*-tolyl-iodonium bromide	2665-60-3			Phenyl-*p*-tolyl-	I^-	56391-18-5	160–162	34
Iodo-o-tolyl diacetate	31599-59-4	Benzene	71-43-2	Phenyl-o-tolyl-	Cl^-	59907-04-9	177–178	30
Iodo-o-tolyl diacetate	31599-59-4	Benzene	71-43-2	Phenyl-o-tolyl-	Br^-	38821-84-0	203–205	37
Phenyl-o-tolyl-iodonium bromide	38821-84-0			Phenyl-o-tolyl-	I^-	59907-07-2	155–156	69
Iodosobenzene diacetate		Mesitylene	108-67-8	Mesitylphenyl-	Cl^-	37567-18-3	162–164	43
Iodosobenzene diacetate		Mesitylene	108-67-8	Mesitylphenyl-[g]	Br^-		155–157[e]	48
Iodosobenzene diacetate		Mesitylene	108-67-8	Mesitylphenyl-	I^-	59907-06-1	137–140	26
Iodosobenzene diacetate		*m*-Xylene	108-38-3	Phenyl-2,4-dimethylphenyl-	Cl^-	59907-07-2	175–177	46
Iodosobenzene diacetate		*m*-Xylene	108-38-3	Phenyl-2,4-dimethylphenyl	Br^-	2014-20-2	169–171	64
Iodosobenzene diacetate		*m*-Xylene	108-38-3	Phenyl-2,4-dimethylphenyl-	I^-	59907-08-3	153–154	66
Iodosobenzene diacetate		*p*-Xylene	106-42-3	Phenyl-2,5-dimethylphenyl-	Cl^-	59907-09-4	171–172	79
Iodosobenzene diacetate		*p*-Xylene	106-42-3	Phenyl-2,5-dimethylphenyl-	Br^-	59907-10-7	174–175	73
Iodosobenzene diacetate		*p*-Xylene	106-42-3	Phenyl-2,5-dimethylphenyl	I^-	59907-11-8	155–157	76

[a] Basis for calculation of yield; all other yields are based on amount of starting compound. [b] Lit. mp 185,[3] 180,[9] 191–192 °C.[26] [c] Lit. mp 162.5–163.5,[3] 168–169 °C.[26] [d] Lit. mp 176–177,[3] 183–184 °C.[7] [e] Lit. mp 170–172 °C.[4] [f] Registry number, 53904-18-0. [g] Registry number, 38821-85-1.

Table II. Pyrolysis of Diaryliodonium Halides at 235 ± 3 °C

Iodonium halide		Products	% pathways for anions[a] Cl^-	Br^-	$^{131}I^-$
4-$CH_3C_6H_4IPh$ X^-	path I	PhI + 4-$CH_3C_6H_4X$	37 (1.8)[b]	34 (1.4) (38.2)[d]	39
	path II	PhX + 4-$CH_3C_6H_4I$	63[c]	66 (61.8)[d]	61
2-$CH_3C_6H_4IPh$ X^-	path I	PhI + 2-$CH_3C_6H_4X$	84 (1.9)	87 (1.5) (86.7)[d]	65
	path II	PhX + 2-$CH_3C_6H_4I$	16	13 (13.3)[d]	35
2,4-$(CH_3)_2C_6H_3IPh$ X^-	path I	PhI + 2,4-$(CH_3)_2C_6H_3X$	72 (2.4)	73 (3.3)	57
	path II	PhX + 2,4-$(CH_3)_2C_6H_3I$	28	27	43
2,5-$(CH_3)_2C_6H_3IPh$ X^-	path I	PhI + 2,5-$(CH_3)_2C_6H_3X$	86 (1.6)	86 (0.9)	68
	path II	PhX + 2,5-$(CH_3)_2C_6H_3I$	14	14	32
2,4,6-$(CH_3)_3C_6H_2IPh$ X^-	path I	PhI + 2,4,6-$(CH_3)_3C_6H_2X$	95 (1.5)	96 (0.3) (96.5)[d]	84
	path II	PhX + 2,4,6-$(CH_3)_3C_6H_2I$	5	4 (3.5)[d]	16
4-$CH_3OC_6H_4IPh$ X^-	path I	PhI + 4-$CH_3OC_6H_4X$		44 (1.8)[e]	19
	path II	PhX + 4-$CH_3OC_6H_4I$		56	81
2,3,5,6-$(CH_3)_4C_6HIPh$ X^-	path I	PhI + 2,3,5,6-$(CH_3)_4C_6HX$		97.7[d]	
	path II	PhX + 2,3,5,6-$(CH_3)_4C_6HI$		2.3	

[a] Average of six runs for chlorides and bromides, one run for iodide-131. [b] Standard deviation. [c] Path II by difference. [d] Reference 5. [e] Average of 12 runs.

group in the para position and no ortho methyl group, the amount of halobenzene produced from the halide ion and of substituted iodoaryl compound (path II) was greater than the amount of iodobenzene and anion-substituted aryl compound (path I). On the other hand, introduction of an ortho methyl group reversed the major direction of decomposition from path II to path I, with the anion-substituted aryl and iodobenzene predominating. As the number of ortho methyl groups was increased to two, so did the yields of products arising from path I.

While the amount of anion-substituted aryl compound (path I) was essentially the same for both chloride and bromide ions for all of the iodonium cations, the amount of products produced by path I decreased somewhat when the anion was iodide-131, except for the phenyl-*p*-tolyliodonium cation. A considerably more marked decrease in products from path I was observed in going from phenyl-*p*-anisyliodonium bromide to its iodide-131, 44% to 19%, respectively. Sandin[9] has reported a value of 12% for the bromide salt; however, we have rechecked our value, for a total of 12 runs, and believe it to be correct.

Discussion

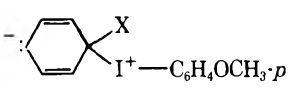
The product compositions clearly preclude a mechanism involving free radicals. First, small quantities of biaryls would be expected to be formed from such a process, and none were found in any of the pyrolysates. Further, a free-radical mechanism will not show a significant dependence upon substituents on the aryl rings,[12,13] and our results and those reported in the literature[5,7] show that there is indeed a substituent effect. For example, even phenyl-*p*-tolyliodonium bromide gave 34% iodobenzene and *p*-bromotoluene (path I), while *p*-tolyl-*p*-nitrophenyliodonium bromide[7] gave only a 4% yield of *p*-nitroiodobenzene and *p*-bromotoluene (path I).

Another mechanistic pathway might be the initial decomposition of the iodonium cation into an areneonium ion and an aryl halide (eq 3).

$$\overset{+}{\text{ArI}}\text{Ar}' \longrightarrow \text{Ar}^+ + \text{Ar}'\text{I} \xrightarrow{X^-} \text{ArX} \qquad (3)$$

In this case the major products formed would be expected to follow the order of stability of the incipient areneonium ions formed, namely, mesitylonium the most followed by xyleneonium, tolueneonium, and benzeneonium in that order. For instance, the pyrolysis of phenyl-*p*-tolyliodonium halides should yield as major products iodobenzene and *p*-halotoluenes. Instead, these products are formed in only 14–32% yields, depending upon the halide ion. Also, phenyl-*p*-anisyliodonium halides should give predominantly iodobenzene and *p*-haloanisoles, but these actually are formed in lesser amounts.

With the exception of the amounts of products obtained from the pyrolysis of ortho methyl substituted iodonium salts, the data are consistent with a nucleophilic aromatic substitution (SN) mechanism as proposed by Yamada.[7] In all cases, the halide ion preferentially attacks the aryl ring best able to accommodate a developing negative charge. For example, if halide ion were to attack the phenyl-*p*-anisyliodonium cation in this manner, formation of *p*-iodoanisole and bromobenzene (path II) would be expected to predominate over that of *p*-bromoanisole and iodobenzene (path I), since the phenyl group would be able to accommodate negative charge development better than would the *p*-anisyl group. This is clear from the resonance structures 3 and 4. The methoxyl group,



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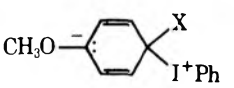

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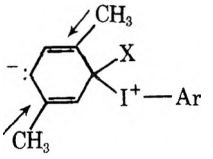
being electron donating in nature, would oppose negative charge development in **4**.

The anomalous ortho methyl effect has previously been accounted for on the basis of formation of an aryl cation.[5] However, the product compositions from pyrolysis of the phenyl-2,4-dimethyl- and phenyl-2,5-dimethylphenyliodonium halides do not support this conclusion. With all halide ions, the 2,4-dimethylphenyl group gave *less* anion-substituted aryl compound (path I) than did the 2,5-dimethylphenyl group.

These data are consistent with an SN-type mechanism, since under these circumstances the 2,5-dimethylphenyl group would accommodate the developing negative charge better than the 2,4-dimethylphenyl group as shown by resonance structures **5** and **6**. In **5** the electron-donating effect of the



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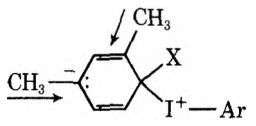
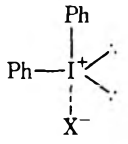


6

3-methyl group is one carbon atom removed from developing negative charge at the para position; hence this methyl group will be less destabilizing in **5** than will the 4-methyl group in **6**.

The structure of diphenyliodonium halides is thought to be trigonal bipyramidal (**7**), with one phenyl ring and the two lone electron pairs occupying the equatorial positions and the other phenyl ring and halide ion at the apical positions.[14] Such a structure has also been reported for iodobenzene dichloride (**8**)[15] and aryl-2-thienyliodonium halides (**1**).[6] On the basis of



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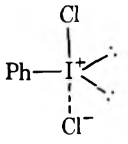

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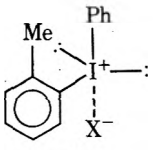
these structures, substituted diaryliodonium halides should have a similar structure. Since the equatorial positions are roomier than the axial positions, it is reasonable that a bulkier group would preferentially occupy one of these, rather than a more crowded axial position. Introduction of one or more ortho methyl groups would considerably increase the "bulk" of an aryl group, increasing the tendency for it to occupy an equatorial position (**9**). This effect would increase with the



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number of ortho methyl groups present. In this configuration, only the group which is equatorial is capable of reacting with the halide ion, the axial group being too distant.[6] The steric crowding of the ortho methyl group(s), then, must be of sufficient magnitude to force the ortho-substituted aryl group into a reactive equatorial position, even though electronic factors governing an SN reaction would dictate that the ring bearing the least number of electron-donating groups be attacked.

That this ortho effect is primarily steric is shown by comparison of the product percentages obtained from pyrolysis of phenyl-*o*-tolyl- and phenyl-2,5-dimethylphenyliodonium halides, which both have one ortho methyl group and about the same electronic requirements. These decompose by path

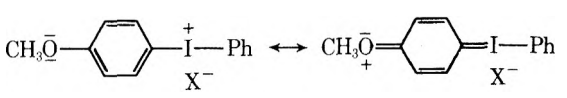
I, respectively; chlorides, 84% and 86%; bromides, 87% and 86%; and iodides, 65% and 68%. When steric requirements are the same and electronic requirements are different, as in the case of the phenyl-2,4-dimethylphenyl- and phenyl-2,5-dimethylphenyliodonium halides, mentioned previously, electronic factors become important.

Aryl-2-thienyliodonium halides decompose upon heating to give as major products an aryl halide derived from the halide ion and 2- iodothiophene.[6] Although this effect has been accounted for on the basis of interaction between the halide ion and the thienyl group, it can also be rationalized on the basis of steric effects. An aryl group, being larger than the 2-thienyl group, would be expected to occupy the roomier, and reactive, equatorial position as in I.

The effect of different halide ions upon product quantities in the pyrolysis of iodonium halides is markedly different from that for pyrolysis of sulfonium halides. In the case of the latter, the amount of 2-halo-*p*-xylene produced from phenyl-*p*-tolyl-2,5-dimethylphenylsulfonium halides increased as the size of the halide ion increased. By contrast, in all series of iodonium halides bearing one or two ortho methyl groups, changing from chloride to bromide ion produced little difference in product quantities, while substitution of iodide ion gave a noticeable *decrease* in the amounts of anion-substituted aryl compound (path I). These observations indicate that, although halide ion is believed to attack the positive sulfur atom to form a tetracovalent intermediate in the pyrolysis of triarylsulfonium salts, formation of an analogous tricovalent iodine intermediate probably does not occur. The decrease in products formed by path I when iodide ion is used can be accounted for nicely by an SN mechanism, since attack of a large iodide ion at a site on the ring adjacent to a methyl group would be expected to be hindered.

This difference in mechanism between the two onium compounds is also consistent with the difference in polarity between the S–X and I–X bonds. In the series of diphenyliioonium halides, the I–Cl bond is the most covalent and the I–I bond the most ionic.[16] Although this order is not known with certainty for the S–X bond in triarylsulfonium salts, the chlorides and bromides are quite ionic. The iodides, however, are much less so, as evidenced by their poor solubility in water and their ir and uv spectra.[17] In chloroform, triphenylsulfonium iodide forms a charge-transfer complex even at low concentrations. The chlorides and bromides do not.[18] It is reasonable, then, that the tendency to form a tetracovalent intermediate in the pyrolysis of sulfonium halides should be greatest with iodide ion since the S–I bond is already partly formed. Conversely, the tendency to form a tricovalent iodine intermediate should be least with iodide ion, since the covalent character of the I–I bond is initially low.

The marked decrease in the products obtained from path I in the pyrolysis of phenyl-*p*-anisyliodonium bromides and iodides-131 (44 and 19%, respectively) can also be accounted for on the basis of differences in polarity of the I–Br and I–I bonds. Resonance interaction of the nonbonded electrons on the *p*-methoxyl group with the positive iodine atom (**10**) has



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been shown to be important.[19] This interaction should increase as the positive character of the iodine atom is intensified, giving more double bond character to the iodine–anisyl group bond and thus making it stronger.[6] Thus, the greater polarity of the I–I bond would result in a stronger iodine–anisyl group bond and in a lesser tendency for successful attack of iodide ion there.

Experimental Section

General. All melting points are uncorrected and were taken using a Mel-Temp apparatus. Iodonium halides decompose upon heating and their apparent melting points depend strongly upon heating rate. The method reported by Beringer[3,4] was used.

Infrared spectra were obtained using a Beckman IR-20A spectrophotometer and an end window G-M counter was used for the iodine-131 determinations. Peracetic acid (40%) was obtained from FMC Corp., Newark, Calif.

Gas chromatographic analyses were performed on an F & M Model 700 gas chromatograph (thermal conductivity detectors). A 6 ft × 0.125 in. stainless steel 10% Carbowax 20M column was used in separation of pyrolysis products except for the pyrolysates of mesitylphenyliodonium chloride and phenyl-2,4-dimethylphenyliodonium bromide and chloride. In these cases, the liquid phase was W98 silicone rubber. Preparative GC separation of the pyrolysis products of the iodonium iodides-131 was accomplished using a 6 ft × 0.25 in. stainless steel 20% Carbowax 20M column. In all cases the support was Chromosorb W.

Iodosobenzene. By treatment with chlorine in cold, dry chloroform iodobenzene was converted to iodobenzene dichloride,[20] which was hydrolyzed with aqueous sodium hydroxide to iodosobenzene.[21]

Iodobenzene Diacetate. Iodobenzene diacetate was prepared by treating iodobenzene with 40% peractic acid and acetic acid.[22]

Iodo-*o*-tolyl Diacetate. This compound was prepared by a procedure similar to that given for iodo-*m*-chlorophenyl diacetate.[23] To 22 g (0.10 mol) of *o*-iodotoluene chilled in an ice bath was added dropwise with stirring 32 ml (0.25 mol) of 40% peracetic acid. Stirring was continued for an additional 2 h, whereupon white crystals formed. The mixture was chilled for 1 h (ice bath), filtered, washed with cold water, and allowed to dry, giving 24 g (70%) of iodo-*o*-tolyl diacetate, mp 143–147 °C (lit.[5] 145–148 °C).

Phenyl-*p*-anisyliodonium Bromide. The method of Beringer[3] was used for the preparation of this compound. An 80% yield of phenyl-*p*-anisyliodonium bromide, mp 176–178 °C (lit.[3] 185 °C), was obtained.

Phenyl-*p*-anisyliodonium Iodide. Addition of excess KI to 6.0 g (15 mmol) of phenyl-*p*-anisyliodonium bromide dissolved in 1.5 l. of ethanol precipitated 4.8 g (11 mmol, 65%) of phenyl-*p*-anisyliodonium iodide, mp 173–174 °C (lit. 162.5–163.5,[3] 175.[4] 204–208,[24] 168–169 °C[24]).

Phenyl-*p*-anisyliodonium Chloride. Attempts to prepare this salt by treatment of phenyl-*p*-anisyliodonium iodide in chloroform with chlorine[25] or by use of iodobenzene diacetate resulted in oils or solids of insufficient purity to be used.

Phenyl-*p*-tolyliodonium Bromide. To a well-stirred suspension of 30.7 g (95.4 mmol) of iodobenzene diacetate and 15.3 g (165 mmol) of toluene in 1000 ml of acetic anhydride kept below 10 °C was added dropwise 50 ml of concentrated H_2SO_4. Stirring was continued for 1 h and the mixture allowed to stand overnight at room temperature. The reaction mixture was then added dropwise to 400 ml of ice water contained in an ice bath and the resulting aqueous solution was extracted twice with 200-ml portions of ether. Treatment of the aqueous phase with 190 g of NaBr produced white crystals when the mixture was allowed to stand overnight. These crystals were collected by filtration and recrystallized from ethanol to yield 20.4 g (57%) of pure phenyl-*p*-tolyliodonium bromide, mp 169–172 °C (lit. 176–177,[3] 183–184 °C[7]).

Phenyl-*o*-tolyliodonium Bromide. To a well-stirred cold mixture of 41.4 g (123 mmol) of iodo-*o*-tolyl diacetate and 50 ml (360 mmol) of benzene in 500 ml of acetic anhydride was added dropwise 50 ml of concentrated sulfuric acid. Stirring was continued for 1 h and the mixture allowed to stand overnight at room temperature, whereupon it was added dropwise to 500 ml of ice water on an ice bath. The resulting aqueous solution was extracted twice with 250-ml portions of ether and treated with 130 g of NaBr in 400 ml of water. Upon standing, white crystals formed which were collected by filtration, washed with water, and dried to give 17.7 g (37%) of phenyl-*o*-tolyliodonium bromide, mp 203–205 °C (lit. 205–210,[4] 167 °C[5]).

Other Arylphenyliodonium Bromides. The other arylphenyliodonium bromides listed in Table I were prepared in the same manner as described for phenyl-*p*-tolyliodonium bromide.

Phenyl-*p*-tolyliodonium Chloride. To a well-stirred, cold solution of 9.47 g (29.4 mmol) of iodobenzene diacetate and 10.0 g (109 mmol) of toluene in 100 ml of acetic anhydride was added dropwise 10 ml of concentrated H_2SO_4. Stirring was continued for 1 h below 10 °C, and the mixture was allowed to stand overnight at room temperature, after which it was added dropwise to 200 ml of ice water contained in an ice bath. A pale yellow solution resulted which was

extracted twice with 100-ml portions of ether. The aqueous layer was treated with 10 g of NaCl dissolved in 100 ml of water and the resulting white crystals were collected by filtration and washed with water and acetone to give 5.12 g (53%) of pure phenyl-*p*-tolyliodonium chloride, mp 197–199 °C.

Phenyl-*o*-tolyliodonium Chloride. To a well-stirred, cold suspension of 9.63 g (28.6 mmol) of iodo-*o*-tolyl diacetate and 10.0 ml (113 mmol) of benzene in 100 ml of acetic anhydride was added dropwise 10 ml of concentrated H_2SO_4. Stirring was continued for 1 h and the mixture was allowed to stand overnight at room temperature. The reaction mixture was then added dropwise to 200 ml of ice water contained in an ice bath and the resulting solution was extracted twice with 100-ml portions of ether. The aqueous phase was treated with 10 g of NaCl dissolved in 50 ml of water, and the white precipitate which formed was filtered, washed, and dried to give 2.89 g (30%) of phenyl-*o*-tolyliodonium chloride, mp 177–178 °C.

Other Arylphenyliodonium Chlorides. The other arylphenyliodonium chlorides listed in Table I were prepared in the same manner as described for phenyl-*p*-tolyliodonium chloride.

Phenyl-*p*-tolyliodonium Iodide. A saturated solution of 10.2 g (27.2 mmol) of phenyl-*p*-tolyliodonium bromide in ethanol was treated with excess KI to give a precipitate of 3.90 g (34%) of phenyl-*p*-tolyliodonium iodide.

Other Arylphenyliodonium Iodides. The other arylphenyliodonium iodides listed in Table I were prepared by metathesis of the appropriate bromide salt in the same manner as for phenyl-*p*-tolyliodonium iodide.

Preparation of Labeled Iodonium Iodides. A ~20% aqueous KI solution was spiked with iodide-131. This solution was used to prepare the labeled iodonium iodides by metathesis of the appropriate iodonium bromides in ethanol.

Proof of Structure. Infrared spectra were in accord with the structure of the aromatic systems of the respective iodonium halides. In a series of halides for a given salt, the spectra were similar.

Pyrolysis products were identified using GC retention times. All of the iodonium salts, when pyrolyzed, gave the products expected from their thermal decomposition, and in no case was any significant amount of unexpected product found.

Product Compositions, Chlorides and Bromides. All of the iodonium chlorides and bromides listed in Table I were pyrolyzed for 5 min at 235 ± 3 °C in 6-mm Pyrex tubes about 30 cm long sealed at one end. Only about 2 cm of the sealed end of the tube was immersed in the oil bath, the remainder of the tube acting as an air condenser. Six runs were made for each individual salt, except in the case of phenyl-*p*-anisyliodonium bromide, where 12 runs were made.

All of the gas chromatograms obtained had sufficient resolution and peak shape to permit calculation of the amounts of aryl halides contained in the pyrolysates. Areas of the peaks were obtained by multiplying the peak height by the peak width at half height, and were corrected for differences in detector sensitivity. The results of these analyses are given in Table II.

Pyrolysis of Iodonium Iodides Labeled with Iodide-131. The pyrolysis products were collected by preparative GC, weighed (approximately 0.1 g), and counted in an end window G-M counter. Because of limited amounts of materials only one sample of each labeled salt was used. The data, presented in Table II, are probably good to ±2%.

Registry No.—Iodobenzene, 591-50-4; o-iodotoluene, 615-37-2; peracetic acid, 79-21-0; acetic acid, 64-19-7; acetic anhydride, 108-24-7.

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Kinetics and Mechanism of Benzylation of Anilines

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Second-order rate constants for the reactions of benzyl halides (Cl, Br, I) and some para-substituted benzyl chlorides (OCH_3, CH_3, Cl, NO_2) with substituted anilines (*p*-OCH_3, *p*-CH_3, H, *p*-Cl, *m*-Cl) were measured in ethanol solution. The reactivity order found for benzyl halides (I > Br > Cl) is in accord with the leaving group polarizability. The reaction rate is increased by electron-donating substituents and decreased by electron-withdrawing ones, both in the nucleophile and in the substrate. Hammett plots are linear on varying the substituents in the aniline, but show remarkable curvature on varying those in the benzyl chloride. The reaction can be adequately described as an SN2 bimolecular process. The reaction rate depends on the electronic availability on the nitrogen atom (bond making) and on the mesomeric interaction between the substrate substituent and the reaction center, which favors the halogen displacement (bond breaking). Electron-donating (electron-withdrawing) groups make the transition state looser (tighter). The C–halogen bond breaking is more advanced with respect to the C–N bond formation.

Solvolytic and nucleophilic reactions of benzyl halides can proceed through an unimolecular, bimolecular, or mixed substitution mechanism, depending on the solvent polarity and on the substrate and nucleophile structures.[1] Benzylation of tertiary amines (Menschutkin reaction) was widely studied and it has long been regarded as one of the best examples of

Table I. Second-Order Rate Constants and Activation Parameters for the Reactions of Benzyl Halides with Aniline in Ethanol[a]

Halide	$k_2 \times 10^3$, l. mol^{-1} s^{-1} 40 °C	50 °C	60 °C	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, cal mol^{-1} K^{-1}
Cl	0.0655	0.142	0.267	14.0	−33.0
Br	3.06	6.13	10.0	11.6	−33.2
I	8.55	17.4	24.4	10.6	−34.2

[a] The estimated precision is ±6% for k_2, ±0.6 kcal mol^{-1} for $\Delta H^{\ddagger}$, and ±3 cal mol^{-1} K^{-1} for $\Delta S^{\ddagger}$ values.

solvent effects on reaction rates,[2-5] but the reaction with primary or secondary amines has not been examined to the same extent.

Peacock[6] and Baker[7] measured respectively the reaction rates of benzyl chloride with some substituted anilines and those of some substituted benzyl halides with aniline, in different experimental conditions. Radhakrishnamurti and Panigrahi[8] correlated the reaction rates of benzyl chloride and bromide with substituted anilines by linear free energy relationships. Recently, Saksena and Bose[9] studied the activation parameters of the benzylation of various mono- and disubstituted anilines in ethanol and in nitrobenzene solutions.

Notwithstanding these results, the lack of a systematic investigation of the substituent effect (both in the nucleophile and in the substrate) and of the leaving group role is evident. The variety of the experimental conditions, in fact, does not allow homogeneous comparisons of kinetic data. Moreover, the reaction mechanism is not yet clarified, Radhakrishnamurti and Panigrahi proposing a transition state symmetrical in the timing of bond making and bond breaking,[8] while Haberfield and co-workers, for the analogous reaction of benzyl halides with pyridine, suggest a transition state shifted toward products.[4]

Following studies on the reactivity of some chloromethyl derivatives with aniline,[10,11] in this paper we report a kinetic study on the substituent and the leaving group effects in the reactions of benzyl halides with anilines in ethanol, to provide a homogeneous set of data and to obtain further informations on the reaction mechanism.

Results and Discussion

Benzyl halides and anilines yield quantitatively *N*-benzylanilines, according to eq 1.

$$p\text{-}YC_6H_4CH_2X + 2ZC_6H_4NH_2 \rightarrow \rightarrow p\text{-}YC_6H_4CH_2NHC_6H_4Z + ZC_6H_4NH_2 \cdot HX \quad (1)$$

X = Cl, Br, I; Y = H; Z = *p*-OCH_3, *p*-CH_3, H, *p*-Cl, *m*-Cl

X = Cl; Y = OCH_3, CH_3, Cl, NO_2;

Z = *p*-OCH_3, *p*-CH_3, H, *p*-Cl, *m*-Cl

The kinetics were done in 99.5% ethanol by titration of the acid produced in the reaction 1 (see Experimental Section). The reactions, carried out in a large excess of aniline with respect to substrate concentration,[12] follow a pseudo-first-order kinetics to at least 75% completion. k_{obsd} values are linearly correlated with the nucleophile concentration, indicating that the reaction is second order overall, first order with respect to each reactant, according to eq 2.

$$k_{obsd} = k_2[C_6H_5NH_2] \quad (2)$$

Second-order rate constants were calculated from the slope of the plot of k_{obsd} vs. aniline concentration, obtained from four to six kinetic runs. The intercept of these plots is practically zero, indicating that the solvolysis reaction is negligible, also for extremely reactive substrates (e.g., *p*-methoxybenzyl chloride, benzyl bromide and iodide).

Table I reports k_2 values and activation parameters for the reactions of benzyl halides with aniline.

The relative rates 2.9/1.0/0.023, respectively, for benzyl iodide/bromide/chloride (with aniline at 50 °C) are almost coincident with the average values reported for other nucleophilic reactions in protic solvents.[13] The activation parameters indicate that the greater reactivity observed for benzyl iodide and bromide with respect to benzyl chloride is ascribed to the more favorable change in enthalpy, the entropy change being constant within experimental errors.

The k_I/k_{Cl} ratio increases with increasing the basicity of nucleophile (Table II), varying from 64 for the reactions with *m*-chloroaniline to 147 for those with *p*-anisidine. A hypothesis based on the hard and soft acids and bases (HSAB) principle[14] might be useful to interpret this trend.

In fact the k_I/k_{Cl} ratio for the reactions of methyl iodide and chloride with hard nucleophiles (CH_3O^-, amines) in protic solvents is about 40 and increases when the substrates react with softer nucleophiles (k_I/k_{Cl} = 150 with N_3^-; k_I/k_{Cl} = 600 with SCN^-). The symbiotic effect then makes the iodide anion a better leaving group with respect to the chloride.[15]

In our case, the saturated carbon atom bearing a softer leaving group, namely in the benzyl iodide, should be better attacked by a softer nucleophile. *p*-Anisidine, owing to its easily polarizable valence electrons, is a softer base with respect to other anilines;[16] hence the enhancement of the k_I/k_{Cl} ratio.

Table II reports second-order rate constants at 50 °C for the reactions of para-substituted benzyl chlorides, benzyl

Table II. Second-Order Rate Constants ($k_2 \times 10^4$, l. mol^{-1} s^{-1}) for the Reactions of *p*-$YC_6H_4CH_2X$ + $ZC_6H_4NH_2$ in Ethanol at 50 °C[a]

X	Y	Registry no.	Z: *p*-OCH_3[b]	*p*-CH_3[c]	H[d]	*p*-Cl[e]	*m*-Cl[f]	ρ Hammett
Cl	OCH_3	824-94-2	48.5	45.1	26.2	24.4	21.5	−0.59
Cl	CH_3	104-82-5	6.10	5.85	3.82	2.46	2.35	−0.73
Cl	H	100-44-7	3.00	2.19	1.42	1.12	0.761	−0.87
Cl	Cl	104-83-6	2.85	2.49	1.56	0.863	0.582	−1.24
Cl	NO_2	100-14-1	2.11	1.27	0.749	0.361	0.190	−1.55
Br	H	100-39-0	163	93.7	61.3	28.9	19.3	−1.40
I	H	620-05-3	442	279	174	80.0	48.6	−1.46
k_I/k_{Cl}			147	127	123	71	64	

[a] The estimated precision of k_2 values is ±6%. [b] Registry number, 104-94-9. [c] Registry number, 106-49-0. [d] Registry number, 62-53-3. [e] Registry number, 106-47-8. [f] Registry number, 108-42-9.

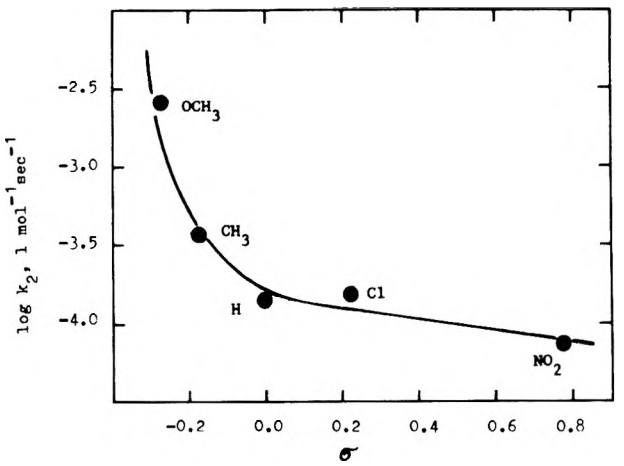

Figure 1. Hammett plot for the reactions of para-substituted benzyl chlorides with aniline in ethanol at 50 °C.

bromide and iodide with substituted anilines. The variation of nucleophilicity with para substituents in the aniline is as expected.[7,8,17] A linear correlation is obtained between log k_2 and Hammett σ.

The ρ values (Table II) depend on the substrate reactivity: the more (less) reactive is the substituted benzyl chloride, the lower (higher) is the reaction sensitivity to substituent effects in the aniline, in agreement with the Hammond postulate and the selectivity principle.[18]

Nevertheless, for the reactions of benzyl halides with anilines, reactivity and selectivity both increase in the order Cl < Br < I. Moreover, for the reactions of *p*-nitrobenzyl chloride and benzyl iodide, where ρ values are almost identical, the reactivity ratio is about 250.

These results confirm that the simultaneous application of the Hammett equation and of the Hammond postulate is not always correct.[19] However, for the benzyl chlorides series, where the reactivity varies within a small range (k_{OCH_3}/k_{NO_2} = 35, with aniline at 50 °C), ρ values might be compared assuming that the transition state structures do not vary meaningfully. The relative reactivities for the benzyl halides, instead (k_I/k_{Cl} = 123, with aniline at 50 °C), already interpreted with the HSAB principle, probably reflect transition states which do not lie in the same position along the reaction coordinate, the comparison of ρ values being not consistent.

The Hammett plots relative to the substituents in the benzyl chlorides show remarkable curvature (Figure 1), analogously to other nucleophilic reactions of substituted benzyl chlorides.[3,20,21] Smooth upward curvature is observed also using σ^+ values, indicating that even Brown's treatment cannot describe adequately the strong effect of mesomeric release from electron-donating substituents to the saturated carbon atom bearing most of the positive charge. The higher reactivity determined by these groups can be ascribed to resonance stabilization of the reaction center, which favors the C–Cl bond breaking.

This trend would be indicative of mechanistic changeover from SN2 to SN1 limit on going from electron-withdrawing substituents to those electron donating,[22] but the reaction was always found to depend on the aniline concentration, also for the reactive *p*-methoxybenzyl chloride, which seems to proceed by a mechanism which is essentially SN2, but not far from the SN1 limit, analogously to the solvolysis reactions.[21]

Electron-donating substituents in the benzyl chloride favor bond breaking, while electron-withdrawing ones favor bond making. Assuming *virtually* separate ρ values for bond making and bond breaking:

$$\rho_{break} < 0 \text{ and } \rho_{mak} > 0$$

In the SN2 transition state bond making and bond breaking are synchronous, and Hammett slope value, which is variable but always negative (Figure 1), indicates the prevailing contribution of the bond breaking on the transition state, which is looser or tighter depending on the substituent effects.

In particular, electron-donating substituents accelerate the chloride ion displacement from the saturated carbon atom more than they decrease nucleophilic attack on it (slope more negative), and electron-withdrawing ones balance the difficulty in the leaving group displacement by favoring the nucleophile attack (slope less negative).

Experimental Section

Starting Materials. Benzyl chloride and its *p*-methyl, *p*-chloro, and *p*-nitro derivatives, benzyl bromide, and the anilines, commercially available samples, were distilled or crystallized before use.

p-Methoxybenzyl chloride[23] was obtained by treatment of *p*-methoxybenzyl alcohol with dry hydrogen chloride, 70% yield, bp 78 °C (1.5 mm).

Benzyl iodide[24] was prepared by reaction of sodium iodide with benzyl bromide, 65% yield, bp 45–46 °C (0.2 mm), mp 28–30 °C.

Ethanol containing 0.5% water (Carlo Erba) was used throughout.

Kinetic Procedure. Rate measurements were done conductometrically by continuous titration of the acid produced with 0.1 M sodium hydroxide, following the procedure already described.[25] The concentration of benzyl halides was about 0.002 mol l.$^{-1}$; aniline concentration ranges were 0.1–0.4 or 0.25–1.0 mol l.$^{-1}$, depending on the substrate reactivity.

Pseudo-first-order rate constants (k_{obsd}, s^{-1}) were obtained from the slope of the conventional plots of log $(a - x)$ vs. time, using the least-squares method.

Reaction Products. Ethanol solutions of benzyl halides (0.05 mol) and anilines (0.1 mol) were refluxed for 2–6 h, depending on the reaction rates. Ethanol was evaporated, and then the residue treated with anhydrous ether; the solution, separated from the anilinium chloride precipitate, was evaporated. The residue was crystallized or distilled under vacuum, yield about 90%.

N-Para-Substituted Benzyl Anilines, *p*-$YC_6H_4CH_2NHC_6H_4Z$ [Y, Z, mp or bp (mm)]: OCH_3, *p*-OCH_3, 97–99;[26] OCH_3, *p*-CH_3, 68;[27] OCH_3, H, 54;[28] OCH_3, *p*-Cl, 69–71;[29] OCH_3, *m*-Cl, 158 (0.1);[29] CH_3, *p*-OCH_3, 68;[29] CH_3, *p*-CH_3, 60;[30] CH_3, H, 47;[30] CH_3, *p*-Cl, 71;[29] CH_3, *m*-Cl, 141–142 (0.3);[29] H, *p*-OCH_3, 50;[28] H, *p*-CH_3, 162–163 (3);[31] H, H, 36–37;[28] H, *p*-Cl, 47–48;[28] H, *m*-Cl, 172–173 (3);[32] Cl, *p*-OCH_3, 69–70;[33] Cl, *p*-CH_3, 47–48;[30] Cl, H, 137–139 (0.3);[34] Cl, *p*-Cl, 70–71;[28] Cl, *m*-Cl, 98;[35] NO_2, *p*-OCH_3, 91;[36] NO_2, *p*-CH_3, 68;[37] NO_2, H, 70;[35] NO_2, *p*-Cl, 97–98;[29] NO_2, *m*-Cl, 62–63.[29]

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Registry No.—*p*-Methoxybenzyl alcohol, 105-13-5.

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A Molecular Orbital Approach to the SRN1 Mechanism of Aromatic Substitution[1]

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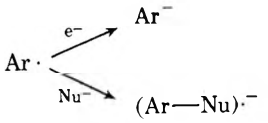
The perturbation molecular orbital approach applied to the reaction of an aromatic radical with an anionic nucleophile gives a good starting point to rationalize the SRN1 mechanism of aromatic substitution. It is shown that there is an attractive molecular orbital interaction between an aromatic radical and a carbanion nucleophile; the strongest interaction occurs at the nucleophile position with highest coefficient in the highest occupied molecular orbital (HOMO). Experimental results suggest that when the nucleophile has two or more equivalent positions (equal coefficients in the HOMO) the coupling occurs at the one which leads to the more stable radical anion as predicted by comparing the energy of the lowest unoccupied molecular orbital (LUMO) of the radical anion intermediate. When the nucleophile is of the type $^{-}CH_2Z$, where Z is an unsaturated moiety, the extra electron in the radical anion intermediate is probably mainly located in the lowest LUMO either in Ar or Z. The body of experimental data to date is in good agreement with the predictions made using this approach.

Chemical reactivity is usually discussed in terms of transition state theory, but in recent years the principles of orbital symmetry,[2] the perturbation molecular orbital, and frontier molecular approaches[3] have been particularly successful in delineating in a simple way those reactions which can occur and in predicting which reaction path is more favorable.

It is a known fact that aryl radicals (Ar·) react with some nucleophiles (Nu^-) at rates which can compete efficiently with the rate of the reaction with solvated electrons (eq 1) as indicated by the product ratio analysis.[4-6]



(1)

As far as we know, there are no kinetic or thermodynamic data available for reactions of Ar· with Nu^-, although it is known that such reactions are quite fast.

It has been shown by the frontier molecular orbital approach that the strongest interaction between two reacting centers occurs through the frontier orbitals of similar energy,[3] so the single occupied molecular orbital (SOMO) of Ar· will interact with the highest occupied molecular orbital (HOMO) of the Nu^-. This interaction will give one two-electrons bonding orbital and only one electron in the antibonding orbital. Assuming that the energy of the SOMO of Ar· and the HOMO of the Nu^- are equal, the change in the π energy as calculated by the first-order perturbation is given by eq 2.[3a]

$$\Delta E\pi = c_{Ar\cdot}^{SOMO} c_{r,Nu^-}^{HOMO} \beta \quad (2)$$

Since $c_{Ar\cdot}^{SOMO} = 1$, eq 2 simplifies to eq 3.

$$\Delta E\pi = c_{r,Nu^-}^{HOMO} \beta \quad (3)$$

If the SOMO of Ar· and the HOMO of Nu^- are not degenerate, the first-order change in π energy is zero. In this case the change in π energy is given by the second-order perturbation for the interaction of atom r of the Nu^- with s of the electrophile which can be calculated by eq 4.[3a]

$$\Delta E\pi = 2\sum_{j}^{occ}\sum_{k}^{unocc} \frac{c_{rj}^2 c_{sk}^2 \beta_{rs}^2}{E_j - E_k} \quad (4)$$

In our particular case where the electrophile is Ar· we have only one orbital with energy close to α and $c_s = 1$; then for the interaction eq 4 simplifies to eq 5.

$$\Delta E\pi = \sum_{j}^{all} \frac{c_{rj}^2 \beta_{rs}^2}{E_j} \quad (5)$$

It follows from eq 5 that the coefficient c_{rj} will determine the position of the coupling. Provided that the predominant term in eq 5 is the one involving the coefficients of the HOMO, this coefficient will determine the most reactive position of the Nu^-.

In the coupling of an Ar· with a carbanionic nucleophile of $^{-}CH_2Z$ type, Ar and Z will not be conjugated in the product, since the two moieties are separated by an sp^3 carbon. Therefore the extra electron must be located in the lowest

unoccupied molecular orbital (LUMO) of either Ar or Z (eq 6).[7]

$$\mathrm{Ar}\cdot + {}^{-}\mathrm{CH_2Z} \begin{cases} \nearrow \mathrm{ArCH_2{-}(Z)}\cdot^{-} \\ \searrow (\mathrm{Ar})\cdot^{-}{-}\mathrm{CH_2{-}Z} \end{cases} \quad (6)$$

We suggest that the radical anion (RA) formed will be that one where the electron is located in the LUMO of lowest energy, which in turn will be the same as the one formed when the neutral product takes an electron (eq 7).

$$\mathrm{Ar{-}CH_2{-}Z} + \mathrm{e}^{-} \begin{cases} \nearrow \mathrm{ArCH_2{-}(Z)}\cdot^{-} \\ \searrow (\mathrm{Ar})\cdot^{-}{-}\mathrm{CH_2{-}Z} \end{cases} \quad (7)$$

Note at this point that we do not mean to say that the RA with lowest energy LUMO is the one formed initially from the reaction of Ar· with $^{-}CH_2Z$. We are referring here to the RA intermediate that predominates in this type of reaction.

No matter which RA is initially formed, a fast equilibrium (eq 8) must be established, and this equilibrium will favor the more stable RA.

$$\mathrm{Ar{-}CH_2{-}(Z)}\cdot^{-} \rightleftharpoons (\mathrm{Ar})\cdot^{-}{-}\mathrm{CH_2{-}Z} \quad (8)$$

ESR studies have shown that this type of equilibrium indeed exists in compounds of type $Ar_1(CH_2)_n(Ar_2)\cdot^{-}$, with $Ar_1 = Ar_2$[8]. Although compounds where $Ar_1 \neq Ar_2$ have not been studied, it is expected that in such a case the equilibrium be shifted toward the more stable RA, considering that in intermolecular electron transfer reactions the equilibrium depicted in eq 9 favors the most stable RA.[9]

$$\mathrm{arene_1} + (\mathrm{arene_2})\cdot^{-} \rightleftharpoons (\mathrm{arene_1})\cdot^{-} + \mathrm{arene_2} \quad (9)$$

In compounds somewhat related to ours, like triptycenes and benzotriptycenes, it has recently been found that the RA formed from electrochemical or alkali metal reduction has the unpaired electron localized in the aromatic ring with largest electron affinity (lowest energy LUMO) with no exchange at all.[10]

On the basis of the ideas outlined above, we will deal next with the experimental facts which give support to them.

Coupling of Phenyl Radical with Hydrocarbon Derived Carbanions. In these reactions phenyl radicals (Ph·) were formed by reaction of monosubstituted benzenes and solvated electrons in liquid ammonia, to give a RA which decomposes to Ph·[11] (eq 10). This radical then reacts with the anionic nucleophile to form a new RA (eq 11), which can transfer its extra electron (eq 12) or take another electron and be reduced (eq 13).[12]

$$\mathrm{PhX} + \mathrm{e}^{-} \longrightarrow (\mathrm{PhX})\cdot^{-} \longrightarrow \mathrm{Ph}\cdot + \mathrm{X}^{-} \quad (10)$$

$$\mathrm{Ph}\cdot + \mathrm{Nu}^{-} \longrightarrow (\mathrm{PhNu})\cdot^{-} \quad (11)$$

$$(\mathrm{PhNu})\cdot^{-} + \mathrm{PhX} \longrightarrow \mathrm{PhNu} + (\mathrm{PhX})\cdot^{-} \quad (12)$$

$$(\mathrm{PhNu})\cdot^{-} + \mathrm{e}^{-} \xrightarrow{\mathrm{NH_3,\ H^+}} \mathrm{PhNuH_2} \quad (13)$$

Pentadienide anion has an energy of α in its HOMO and the coefficients $c_1^H = -c_3^H = c_5^H$, with the charge density in the three carbons being the same.[13] Considering only the coefficients c^H, two products should have been formed, i.e., reaction at carbon 1 and carbon 3.

Pentadienide anion **1** reacts with Ph· giving phenylpentadienes and phenylpentenes,[12] all with the benzene ring attached to carbon 1 (eq 14).[15]

The reaction at carbon 3 would have given the RA **3a** and/or **3b**.

The energy of the LUMO of ethylene is equal to that of

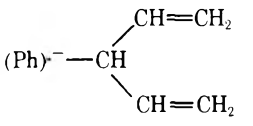
$$\mathrm{Ph}\cdot + (\mathrm{C_1{=}C_2{=}C_3{=}C_4{=}C_5})^{-} \quad \textbf{1}$$

$$\longrightarrow (\mathrm{Ph})\cdot^{-}{-}\mathrm{CH_2{-}CH{=}CH{-}CH{=}CH_2} \quad \textbf{2a}$$

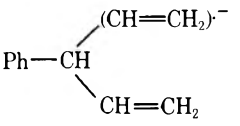
or

$$\mathrm{Ph{-}CH_2{-}(CH{=}CH{-}CH{=}CH_2)}\cdot^{-} \quad \textbf{2b} \quad (14)$$

benzene = -1.000β,[16] whereas the value of the LUMO of the butadiene moiety in the RA **2b** is lower (Table I). We know from the product distribution that the formation of the RA **3a** and **3b** does not compete with RA **2a** or **2b**, but we do not



3a



3b

have any strong evidence as to which of them is formed, although the formation of phenylpentenes might suggest that RA **2b** was formed and reduced in the sense of eq 13. Product distribution has been used previously as a criterion to establish which RA is formed.[5,17]

p-Anisylpropenide anion **4** has c_1^H and $-c_3^H$ almost equal in the HOMO. However, attack of Ph· occurs three times more rapidly at carbon 3 than at carbon 1.[12] For the addition of Ph· at atom 1 of *p*-anisylpropenide, there are three unsaturated systems isolated which can accept the extra electron, forming RA **5a**, **5b**, and **5c**; all of them have the same energy in their LUMO, -1.000β (eq 15).[15]

$$\mathrm{Ph}\cdot + (p\text{-anisyl}{-}\mathrm{C_1{=}C_2{=}C_3})^{-} \quad \textbf{4}$$

$$\longrightarrow (p\text{-anisyl})\cdot^{-}{-}\mathrm{CH}(\mathrm{Ph}){-}\mathrm{CH{=}CH_2} \quad \textbf{5a}$$

$$p\text{-anisyl}{-}\mathrm{CH}(\mathrm{Ph}\cdot^{-}){-}(\mathrm{CH{=}CH_2})\cdot \quad \textbf{5b}$$

$$p\text{-anisyl}{-}\mathrm{CH}(\mathrm{Ph}){-}(\mathrm{CH{=}CH_2})\cdot \quad \textbf{5c} \quad (15)$$

On the other hand, in the reaction at carbon 3, there are two possible RA's: **6a** and **6b** (eq 16).

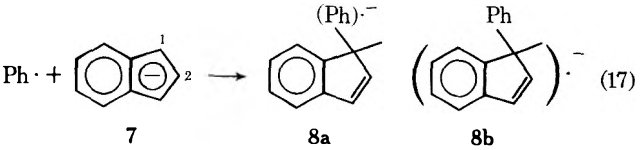
$$(p\text{-anisyl}{-}\mathrm{CH{=}CH})\cdot^{-}{-}\mathrm{CH_2{-}Ph} \quad \textbf{6a}$$

$$p\text{-anisyl}{-}\mathrm{CH{=}CH{-}CH_2{-}(Ph)}\cdot^{-} \quad \textbf{6b} \quad (16)$$

RA **6a** has the extra electron in a LUMO with lower energy than RA **6b**; therefore, it will be preferentially formed.

It follows from the two examples mentioned above that when the coefficients c^H in the nucleophile have the same value, the reaction path followed is that which leads to the RA with the LUMO of lower energy. In other words, although the perturbation theory predicts that all positions in the nucleophile with equal c^H are equally reactive, the stability of the intermediate RA controls the reaction and the thermodynamically more stable product is formed preferentially.

Indene anion **7**, on the other hand, has $c_1^H > c_2^H$, so the attack occurs exclusively at carbon 1 (eq 17).[12]



7 **8a** **8b** (17)

Table I. HMO Values of the Frontier Molecular Orbital of Nucleophiles and Products in Aromatic SRN1 Reactions[a]

Aromatic radical	Nucleophile	Registry no.	Coefficients (HOMO)[b]	Position in the coupling	RA formed	LUMO[c]	Ref
Phenyl	$(C_1\text{-}C_2\text{-}C_3\text{-}C_4\text{-}C_5)^{-d}$	56094-24-7	$c_1H = c_3H$	C_1	2b	0.318	12
Phenyl		12128-54-0	$c_1H \gg c_2H$	C_1	8b	0.362	12
Phenyl	$(p\text{-Anisyl-}C_1\text{-}C_2\text{-}C_3)^{-d}$	40719-29-7	$c_1H = c_3H$	$C_1 < C_3$ (on C_3) (on C_1)	6a 5[e,f]	0.398 1.000	12
Phenyl	$^{-}CH_2COCH_3$	24262-31-5	$c_CH > c_OH$	C_1	10	0.740	5
Mesityl	$^{-}C_1\text{-CO-}^{-}C_3\text{-}COCH_3{}^{d}$	54210-56-9	$c_1H > c_3H$	C_1	12[e]	0.383	22
Phenyl		18860-16-7	$c_1H > c_NH$	C_1	17a[e]	0.367	25
Phenyl	$^{-}CH_2\text{-CN}$	21438-99-3	$c_CH > c_NH$	C_1	19	0.820[g]	26
4-Biphenylyl	$^{-}CH_2\text{-CN}$		$c_CH > c_NH$	C_1	21a	0.705	27
p-Benzoylphenyl	$^{-}CH_2\text{-CN}$	59922-52-0	$c_CH > c_NH$	C_1	21b	0.294	27
2-Quinolyl	$^{-}C_1\text{-CO-}^{-}C_3\text{-COPh}^{d}$		$c_1H > c_3H$	C_1	14a[e] 14b[e]	0.438 0.460	23
2-Pyridyl	$^{-}CH_2\text{-CN}$		$c_CH > c_NH$	C_1	26	0.667	27
1-Naphthyl	$^{-}CH_2COCH_3$		$c_CH > c_OH$	C_1	15	0.618	17
1-Naphthyl	$^{-}CH_2\text{-CN}$		$c_CH > c_NH$	C_1	23	0.618	17
2-Naphthyl	$^{-}CH_2\text{-CN}$		$c_CH > c_NH$	C_1	24	0.618	27
9-Phenanthryl	$^{-}CH_2\text{-CN}$		$c_CH > c_NH$	C_1	25	0.605	27
1-Naphthyl	$^{-}CH_2COPh$	59922-53-1	$c_CH > c_OH$	C_1	16a	0.386	17

[a] Simple Hückel MO method was used in the calculations. The parameters were taken from Streitwieser[14] unless otherwise stated. [b] Coefficients of the highest occupied MO in the nucleophile. [c] The lowest unoccupied MO of the product $ArCH_2Z$ is the single occupied MO in the radical anion. [d] Hydrogen atoms in the nucleophile are omitted for clarity. [e] There is no evidence which radical anion is formed. [f] Any one of the three possibilities (ethylene, benzene, and anisole) have the same LUMO value. [g] Parameters for CN were taken from ref 28.

RA **8b** has the extra electron in a LUMO with lower energy than RA **8a**; therefore, it will be preferentially formed, and the reduction to 1-phenylindan[12] might indicate the reduction of RA **8b** in the sense of eq 13.

Coupling of Aromatic Radicals with Ketone Enolate, Picolyl, and Cyanomethyl Anions as Nucleophiles. Allyl anion has a c_1H equal to $-c_3H$, but when carbon 3 is replaced by a heteroatom, the charge density in the heteroatom (oxygen or nitrogen) is higher than on carbon; however, in the HOMO, c_CH is higher than c_OH or c_NH.

In the reaction of a radical with a bidentate nucleophile, the value of the coefficient of the frontier molecular orbital will determine the position of reaction. This conclusion is supported by the fact that ketone enolate, picolyl, and cyanomethyl anions react only through the carbon with higher cH (Table I).

There is a precedent in aliphatic SRN1,[18] where it was pointed out that the reaction of an aliphatic radical with a bidentate nucleophile is an orbital-controlled reaction.[19]

In the reaction of Ph· with acetonate anion **9** the substitution occurs only on carbon (eq 18).

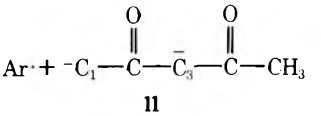
$$Ph\cdot + {}^{-}CH_2COCH_3 \longrightarrow Ph\text{—}CH_2\text{—}(COCH_3)\cdot^{-} \qquad (18)$$

9 **10**

There are experimental indications that **10** is the RA formed,[5,20] in agreement with the LUMO values shown in Table I.[21]

Several cyclic and noncyclic ketone enolate ions have been arylated by this method under photostimulation in liquid ammonia; all of them reacted at the α carbon atom.[22]

Ph· do not react with monoenolate ions of β-dicarbonyl compounds, but 2-bromomesitylene reacted with the dipotassium salt of 2,4-pentadione **11** giving 1-mesityl-2,4-pentadione in 82% yield. The dianion **11** has two nucleophilic centers, carbon 1 and carbon 3, with $c_1H > c_3H$, and the only product obtained was that of reaction on carbon 1 (eq 19).[22]



11

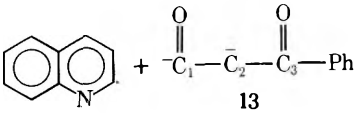
$$\longrightarrow Ar\text{—}CH_2\text{—}(CO\text{—}\bar{C}H\text{—}COCH_3)\cdot^{-} \qquad (19)$$

12

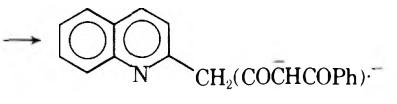
Ar = mesityl

There are few examples of heteroaromatic radicals in reaction with Nu^- by the SRN1 mechanism of aromatic substitution.[23,24] 2-Chloroquinoline reacted with ketonate anions giving substitution products much as phenyl radical does, both stimulated by light or solvated electrons in liquid ammonia.[23]

One example involving benzoylacetone dianion **13** has been reported. This Nu^- has two nucleophilic centers on carbon 1 and on carbon 3, having c_1H higher than c_3H. Accordingly only one substitution product is obtained, namely the one attached to carbon 1 (eq 20).

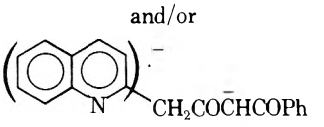


13



14a

and/or

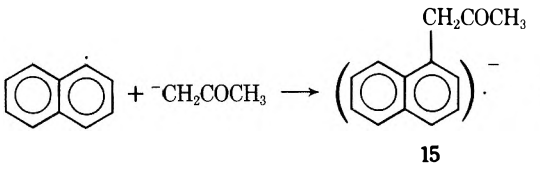


14b

(20)

RA **14a** has a similar value of the energy in the LUMO to **14b**, and there is no evidence as to which RA is formed.

1-Naphthyl radicals react with acetonate anion to give substitution products on carbon as Ph· does, but the extra electron is located on the aromatic moiety and not in the nucleophile, owing to the lower energy LUMO of the naphthalene than the carbonyl group[21] (eq 21).

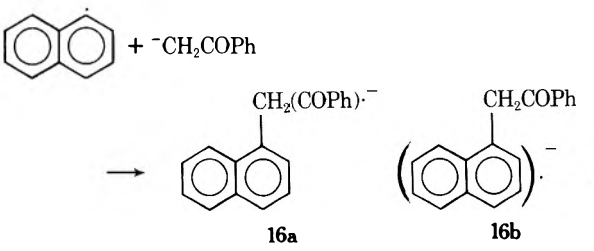


(21)

15

There is experimental evidence for the formation of RA **15** and not the ketyllike RA **10** as in the reaction with Ph·.[17]

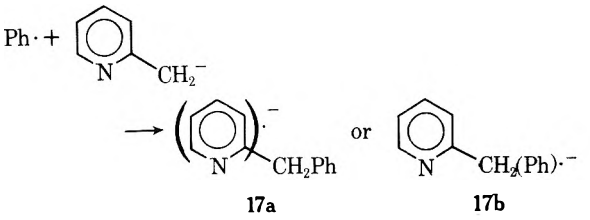
Acetophenone anion is another nucleophile of the type $^{-}CH_2Z$, but where Z = COPh has a lower energy LUMO than naphthalene moiety. As expected in the reaction with 1-naphthyl radical, the RA formed was **16a** instead of **16b** (eq 22).[17]



(22)

16a 16b

With 2- and 4-picolyl anions as nucleophiles, Ph· couples with carbon 1 (higher c^H) (eq 23).[25]

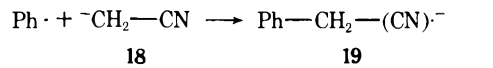


(23)

17a 17b

There are no indications which RA is formed, but RA **17a** has the lowest energy LUMO, which lead us to suggest on the base of the above arguments that RA **17a** and not **17b** is the one formed.

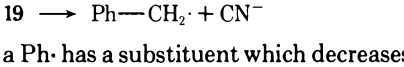
With cyanomethyl anion also the substitution occurs at carbon 1 (higher c^H) and the RA **19** formed is the one with the lowest energy LUMO[28] (eq 24).



(24)

18 19

There is experimental evidence that RA **19** is the intermediate formed predominantly because it decomposes to benzyl radical and cyanide ions (eq 25).[26]



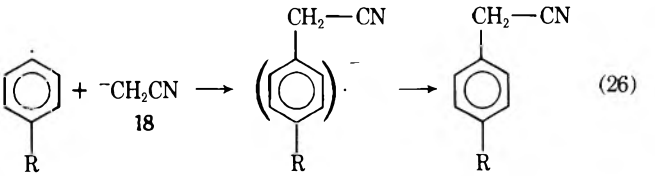
(25)

However, when a Ph· has a substituent which decreases the value of the LUMO of the aromatic moiety, such as **20,** the CN moiety has now higher LUMO than the aromatic moiety, and the RA formed predominantly is **21,** which does *not* suffer C–CN bond breaking. Consequently only the acetonitrile derivatives **22** are formed (eq 26).[27]

It is remarkable that the presence of a substituent R in the phenyl ring which lowers the value of the LUMO of the aromatic moiety can change so dramatically the product distribution.

1-Naphthyl, 2-naphthyl, and 9-phenanthryl radicals also reacted with cyanomethyl anion to give acetonitrile derivatives without C–CN bond rupture (Table I), which means that RA's **23, 24,** and **25** are the intermediates in these reactions.[27]

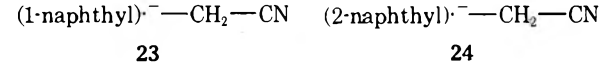
2-Chloropyridine reacts with cyanomethyl anion stimulated by light to give 2-pyridylacetonitrile, and no C–CN bond cleavage was observed.[27] Pyridine has a LUMO value lower than the CN moiety, and again the product distribution depends on which is the lowest LUMO in both moieties (eq 27).



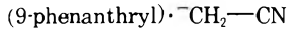
(26)

20 21 22

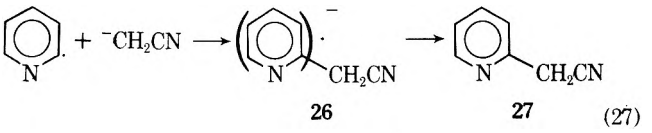
20a, Ph
b, COPh



23 24



25



(27)

26 27

The PMO method applied to the SRN1 mechanism allows one to predict the products to be expected in the reaction of aromatic radicals with ambidentate nucleophiles by simply calculating the coefficients of the HOMO of the reactive atoms of the nucleophile.[29] Moreover when there are several possible radical anion intermediates, consideration of the LUMO's of the groups involved allows one to predict which will be the intermediate that will predominate in the reaction and consequently the products.

We are aware that there are other possible approaches and other factors (solvation, ion pairs, etc.) besides molecular orbital considerations to be taken into account to deal with the problem in a more general way, but the method presented here seems very appropriate to explain the body of experimental data existent in the literature.

Acknowledgment. We thank Dr. W. C. Herndon for reading the manuscript. Molecular orbital calculations were carried out in the Computer Center of the Faculty of Economyc Sciences, Universidad Nacional de Córdoba. Technical assistance by Engineer F. Torres Crespo is gratefully acknowledged.

Registry No.—Phenyl, 2396-01-2; mesityl, 19121-63-2; 4-biphenylyl, 2510-50-1; *p*-benzoylphenyl, 59922-54-2; 2-quinolyl, 54978-39-1; 2-pyridyl, 15905-71-2; 1-naphthyl, 2510-51-2; 2-naphthyl, 10237-50-0; 9-phenanthryl, 20199-82-0.

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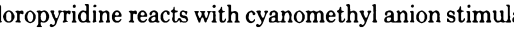

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(15) The hydrogen atoms were omitted in the nucleophile for clarity.
(16) The reader should be reminded that the energies of the MO are represented as a series of energy levels above and below an energy zero taken as α: $E_j = \alpha + m_j\beta$. Since β is negative, negative values of m_j represent energy levels more positive (less stable).
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Photostimulated Arylation of Cyanomethyl Anion by the SRN1 Mechanism of Aromatic Substitution[1]

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The photostimulated reaction of 1- or 2-chloronaphthalenes, 4-chlorobiphenyl, 4-bromobenzophenone, and 2-chloropyridine with cyanomethyl anion in liquid ammonia leads to the formation of α-aryl or hetaryl acetonitrile derivatives in excellent yields, probably by the SRN1 mechanism of aromatic substitution. The photostimulated reaction of bromobenzene with the same nucleophile gives a mixture of phenylacetonitrile, 1,2-diphenylethane, and toluene. The difference in behavior of this latter substrate compared to those reported in this study is postulated to be due to differences in the predominant intermediates formed when an aromatic radical couples with the cyanomethyl anion. These reactions have potential value in synthesis to obtain α-aryl or α-hetaryl acetonitrile derivatives.

The photostimulated reaction of bromobenzene and cyanomethyl anion in liquid ammonia afforded phenylacetonitrile (8%) and 1,2-diphenylethane (18%), together with small amounts of toluene, benzene, and 1,1-diphenylethane.[2] This reaction occurred by the SRN1 mechanism of aromatic substitution,[3] as depicted in Scheme I.

Scheme I

$$\underset{\mathbf{1}}{ArX} + {}^-CH_2CN \xrightarrow{h\nu} \underset{\mathbf{2}}{(ArX)\cdot^-} + \text{residue} \qquad (1)$$

$$\underset{\mathbf{2}}{(ArX)\cdot^-} \longrightarrow \underset{\mathbf{3}}{Ar\cdot} + X^- \qquad (2)$$

$$\underset{\mathbf{3}}{Ar\cdot} + {}^-CH_2CN \longrightarrow \underset{\mathbf{4}}{(ArCH_2CN)\cdot^-} \qquad (3)$$

$$\underset{\mathbf{4}}{(ArCH_2CN)\cdot^-} + \underset{\mathbf{1}}{ArX} \longrightarrow \underset{\mathbf{5}}{ArCH_2CN} + \underset{\mathbf{2}}{(ArX)\cdot^-} \qquad (4)$$

termination steps (5)

When Ar = Ph, other steps are involved, such as 6–8.[2]

$$\underset{\mathbf{4}}{(PhCH_2CN)\cdot^-} \longrightarrow \underset{\mathbf{6}}{PhCH_2\cdot} + CN^- \qquad (6)$$

$$\underset{\mathbf{6}}{PhCH_2\cdot} \longrightarrow Ph{-}CH_2{-}CH_2{-}Ph \qquad (7)$$

$$\underset{\mathbf{6}}{PhCH_2\cdot} \longrightarrow PhCH_3 \qquad (8)$$

However, when the same reaction was carried out with 1-chloronaphthalene, the only product observed was the acetonitrile derivative **5**. No products from the decomposition of the radical anion **4** as in steps 6–8 were found.[4]

The difference in behavior found between the phenyl and naphthyl system was attributed to differences in the predominant intermediate formed in these reactions. The argument as reported previously[5] can be summarized as follows: when an aromatic radical couples with cyanomethyl anion or other carbanionic nucleophiles of the type $^-CH_2Z$ with Z being an unsaturated moiety, the extra electron in the intermediate can be located either in Z or Ar, forming intermediates **4a** and **4b**, depending on which moiety has lower value of the lowest unoccupied molecular orbital (LUMO) (eq 9).

$$\underset{\mathbf{4a}}{Ar{-}CH_2{-}(Z)\cdot^-} \qquad \underset{\mathbf{4b}}{(Ar)\cdot^-{-}CH_2{-}Z} \qquad (9)$$

For instance, when Ar = Ph and Z = CN, the predominant radical anion intermediate resembles structure **4a**, and this intermediate can transfer its extra electron as in step 4 to give ultimately phenylacetonitrile, or can decompose as in step 6 to give benzyl radical **6**. When Ar = 1-naphthyl, the aromatic moiety has a lower LUMO value than the CN moiety, and the structure of the predominant radical anion intermediate is **4b**, which only can transfer its extra electron as in step 4 to give the acetonitrile derivative **5**.

We now report a further study of arylation reactions of

Table I. Photostimulated Arylation of Cyanomethyl Anion in Liquid Ammonia

No.	ArX	Registry No.	M	KCH_2CN M	Time, min	Yield, %[b] ArX[a]	ArH	$ArCH_2CN$
1[c]	Bromobenzene	108-86-1	0.011	0.075	120		*d*	25[e]
2[f]	1-Chloronaphthalene	90-13-1	0.050	0.123	100[g]		4	89[h]
3	2-Chloronaphthalene	91-58-7	0.013	0.074	45		2	98 (93)[i]
4	9-Bromophenanthrene[j]	573-17-1	0.019	0.095	60	31	7	60
5	9-Bromophenanthrene[k]		0.009	0.060	120	14	16	70
6	1-Bromo-2-naphthoxide	59907-41-4	0.022	0.118	60	0[l]	(98)[i]	0[l]
7	Ethyl *p*-chlorobenzoate	7335-27-5	0.013	0.050	60	*d*		
8	*p*-Bromonitrobenzene	586-78-7	0.008	0.041	60	*d*		
9	4-Chlorobiphenyl	2051-62-9	0.016	0.077	20		4	96 (94)[i]
10	4-Chlorobiphenyl[m]		0.007	0.093	5	5	3	92
					15	3	3	94
					35			97 (90)[i]
11	4-Chlorobenzophenone	134-85-0	0.019	0.059	60		*d*	(97)[i]
12	2-Chloropyridine[m]	109-09-1	0.053	0.208	5	5	1	94
					30		1	98 (56)[i]

[a] Starting material recovered. [b] Yields determined by GLC, unless otherwise quoted. [c] Run carried out by A. B. Pierini. [d] Not quantified. [e] 1,2-Diphenylethane was obtained in 53% yield. This is a reaction similar to that reported in ref 2. [f] See ref 4. [g] In another similar experiment, 1-chloronaphthalene reacted quantitatively in less than 15 min. [h] Bis(1-naphthyl)acetonitrile was obtained in 7% yield. [i] Isolated crude product from which pure samples were obtained. [j] Slightly soluble in ammonia. [k] Starting material dissolved in ca. 5 ml of anhydrous diethyl ether. [l] Determined by TLC. [m] Samples were taken after the time indicated.

cyanomethyl anion stimulated by light in liquid ammonia to establish the scope and limitations of these reactions as a synthetic method and to demonstrate to what extent the products may be anticipated provided that the LUMO's of the aromatic and the CN moiety are known.

Results and Discussion

We repeated the reaction of bromobenzene and cyanomethyl anion in liquid ammonia, reported by Bunnett and Gloor,[2] using a different light source (see Experimental Section) and wished to see if this caused any differences in the product composition. Although we obtained better yield (all the bromobenzene reacted in 120 min of irradiation whereas in the paper cited there was as much as 62% of unreacted bromobenzene after 120 min irradiation) the ratio of 1,2-diphenylethane (53%) to phenylacetonitrile (25%) was 2.12, similar to the value of 2.25 found previously.[2]

In an attempt to change the product composition we added catalytic amounts of naphthalene or biphenyl (5–10 mol %) with the expectation that these better electron acceptors would increase the rate of step 4, thereby decreasing the ratio of 1,2-diphenylethane/phenylacetonitrile. However, the reaction was strongly inhibited under these conditions. Inhibition of radical anion chain mechanism as Scheme I is precedented.[6] This inhibition may be also due to an acid–base reaction between phenylacetonitrile and naphthalene radical anion (eq 10–12).

$$(PhCH_2CN)\cdot^- + Naph \longrightarrow PhCH_2CN + (Naph)\cdot^- \quad (10)$$

$$(Naph)\cdot^- + PhCH_2CN \longrightarrow NaphH\cdot + PhCHCN \quad (11)$$

$$NaphH\cdot \xrightarrow{e^-,\ H^+} NaphH_2 \quad (12)$$

A study of the reaction of phenylacetonitrile with naphthalene radical anion in various ether solvents has been reported.[7] It was found that proton abstraction (eq 11) was usually the major reaction pathway.[8]

In the small amounts of products formed, the ratio of 1,2-diphenylethane/phenylacetonitrile had not changed. This phenomenon is not fully understood and more work is being done along this line.

The photostimulated reactions of 2-chloronaphthalene and 9-bromophenanthrene with cyanomethyl anion in liquid ammonia lead to the acetonitrile derivatives **5** in high yields (Table I). No products derived from C–CN bond cleavage were detected by NMR.

With 1-bromo-2-naphthoxide and cyanomethyl anion, we obtained only 2-naphthol, the reduction product (Table I). This result implies that there is a photostimulated electron transfer from the nucleophile to the substrate (step 1) but the radical **3** formed in step 2 does not couple with the cyanomethyl anion (step 3); instead it is reduced to give ultimately 2-naphthoxide. Similarly in the photostimulated reaction of *p*-bromophenoxide with acetone enolate anion in liquid ammonia only the dehalogenation product was obtained.[9] The lack of reactivity can be attributed to the low electrophilicity of an aromatic σ radical bearing an electron-releasing group.

Dehalogenation of haloaromatic compounds by thermal electron transfer from nucleophiles such as methoxide anion has been reported.[10,11]

All the polycyclic condensed hydrocarbons have lower LUMO values than the CN moiety, so we expected that all the halo derivatives would give the α-acetonitrile derivatives in the photostimulated reaction with cyanomethyl anion in liquid ammonia. On the other hand, the benzene ring has a LUMO value higher than the CN moiety as mentioned before, but an appropriate substituent attached to the ring may decrease its LUMO to a value lower than that of the CN moiety, and different reaction products might well be obtained (no C–CN bond cleavage).

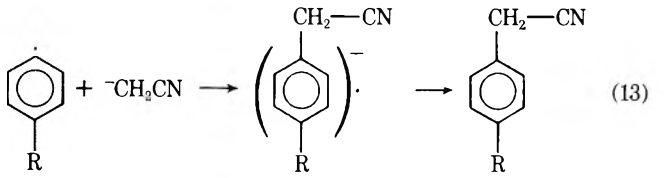
In order to probe our hypothesis, we studied halobenzenes with substituents attached to the ring that decrease the LUMO value of the aromatic moiety. Substituents such as nitro, CO_2Et, C_6H_5, and COC_6H_5 fulfill this requirement.

Unfortunately the photostimulated reaction of *p*-bromonitrobenzene and ethyl *p*-chlorobenzoate with cyanomethyl anion in ammonia did not give substitution or reduction products. Apparently other reactions took place. Nitro-substituted compounds also fail to give photostimulated reaction with acetone enolate anion in ammonia.[9]

The photostimulated reaction of *p*-chlorobiphenyl and *p*-chlorobenzophenene with cyanomethyl anion in ammonia gives the α-acetonitrile derivatives in high yields, and no products derived from C–CN bond cleavage were observed (Table I).

It is remarkable that the presence of a substituent such as C_6H_5 and COC_6H_5 can change the product composition so

dramatically in the reaction of para-substituted phenyl radical with cyanomethyl anion (eq 13).



(13)

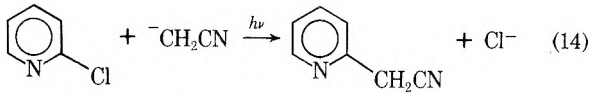
7

R = C_6H_5, COC_6H_5

These results are in agreement with our predictions based on the LUMO's of the aromatic moiety.

Not only may a substituent attached to the benzene ring bring about a lower LUMO value than the CN moiety, but so may replacement of one of the ring carbons by an electronegative heteroatom such as nitrogen, as in the case of pyridine.

Accordingly, we found that the photostimulated reaction of 2-chloropyridine with cyanomethyl anion in ammonia gave 2-pyridylacetonitrile in high yields also without C–CN bond cleavage (eq 14).



(14)

Rate of the Reaction. The photostimulated reaction of bromobenzene with cyanomethyl anion in liquid ammonia is remarkably slower than the reaction with acetone enolate anion.[2,12] The differences in rates were attributed to the important steps (6–8) that interrupt the chain mechanism lowering the overall rate of the reaction.

In a few experiments with 1-chloronaphthalene, 4-chlorobiphenyl, and 2-chloropyridine (Table I), which are substrates where steps 6–8 do not take place, samples were taken after different periods of reaction in order to measure qualitatively the rate of reaction. All of them reacted quantitatively in less than 15 min.

Competition experiments between acetone enolate anion and cyanomethyl anion with 1-chloronaphthalene give no reproducible results (reactivity ratio between 0.5 and 3), but it is evident from these experiments that the reactivities of both anions are very similar. These results indicate that it is not the intrinsic reactivity of acetonitrile which makes the reaction of bromobenzene with acetonitrile anion slower than that of acetone enolate anion, but rather the important steps that interrupt the chain mechanism in the former case.

Synthetic Applications. In view of the results reported here, we conclude that this is an important synthetic method for obtaining α-aryl or hetaryl acetonitrile derivatives (eq 15).

$$ArX + {}^-CHR{-}CN \xrightarrow[NH_3]{h\nu} ArCHR{-}CN + X^- \quad (15)$$

The general conditions necessary to obtain good yields of arylation product are that the aromatic moiety must have a lower LUMO than the CN moiety and must not have an electron-releasing substituent such as O^- or NMe_2 or a substituent that reacts with cyanomethyl anion. Benzene derivatives, polycyclic aromatic hydrocarbons, and heteroaromatic hydrocarbons are suitable substrates.

Experimental Section

General. Melting points have not been corrected. NMR spectra were recorded on a Varian T-60 nuclear magnetic resonance spectrophotometer using CCl_4 as solvent, unless otherwise quoted, and all the spectra are reported in parts per million relative to Me_4Si (δ). Thin layer chromatography was performed on silica gel plates. Gas chromatographic analyses were performed on a Varian Aerograph Series 2400 with flame ionization detector, using a column packed with 3% Silicon Rubber SE-30 on Chromosorb P 80–100, 6 ft × 0.125 in.

Materials. Acetonitrile (BPC Erba) was dried over anhydrous K_2CO_3, refluxed with P_2O_5, and distilled as needed. All the haloaromatic compounds were commercially available and were used as received, except 9-bromophenanthrene[13] and 1-bromo-2-naphthol,[14] which were prepared according to the method described. Liquid ammonia was dried with Na metal and distilled under nitrogen into the reaction flask. Cyanomethyl anion was prepared as described.[2,4]

Photostimulated Reactions. The photostimulated reactions were carried out in a photochemical reactor equipped with two 250-W uv lamps, Philips, Model HTP, emitting maximally at ca. 360 nm, with water jacket refrigeration. The method used was as described.[4] Products were isolated and identified by standard procedures.

Identification of Products. Analyses were performed on pure samples obtained from the crude products. Unreacted starting materials and dehalogenation products were identified and quantified by comparison of their GLC retention time and/or by TLC. Evidence for the identity of other products is now presented.

β-Naphthylacetonitrile was recrystallized from petroleum ether, NMR spectrum identical with that of an authentic sample;[15] 9-phenanthrylacetonitrile recrystallized from petroleum ether, mp 96–97 °C (lit.[16] mp 96.5–97 °C), NMR 3.90 (s, 2 H), 7.38–7.88 (m, 7 H), and 8.28–8.72 ppm (m, 2 H); 4-biphenylacetonitrile, NMR identical with that of an authentic sample;[17] 4-benzoylphenylacetonitrile, recrystallized from petroleum ether, mp 63–64 °C (lit.[18] mp 64 °C), NMR (solvent acetone-d_6) 3.60 (s, 2 H), 7.22–7.90 ppm (m, 9 H); 2-naphthol, TLC (benzene as solvent) R_f 0.29 (1-bromo-2-naphthol has R_f 0.64), NMR identical with that of authentic sample. 2-Pyridylacetonitrile, NMR identical with that described in the literature.[19]

Registry No.—Cyanomethyl, 2932-82-3

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Synthesis, Electronic Spectra, and Thermal Behavior of Bis(heptaphenylcycloheptatrienes)

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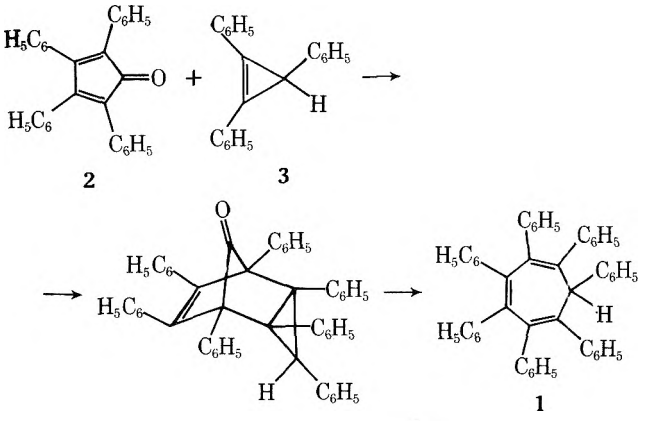
The synthesis of several members of a new class of compounds, the bis(heptaphenylcycloheptatrienes), is reported where the linking groups connecting the two hexaphenylcycloheptatriene moieties include phenyl, diphenyl, diphenylmethane, and diphenyl ether. The electronic spectral behavior of the bis(heptaphenylcycloheptatrienes) shows that the major chromophore of these compounds is an individual heptaphenylcycloheptatriene moiety. Differential thermal analysis shows two or more endotherms for each bis(heptaphenylcycloheptatriene) in the range 430–656 °C with indications of liquid crystal behavior. Comparison of the thermal behavior of these compounds with that of the parent heptaphenylcycloheptatriene is also discussed.

The synthesis of a wide variety of polyphenylated hydrocarbons has been made feasible by the Diels–Alder reaction followed by the decarboxylation reaction of the Diels–Alder adducts.[1] To date the heptaphenylcycloheptatrienes reported have been made via this approach and include the parent 1,2,3,4,5,6,7-heptaphenylcyclohepta-1,3,5-triene (**1**),[2] 1,2,3,4,5,6,7-heptaphenylcyclohepta-1,3,5-trien-7-ol,[3] 7-methoxy-1,2,3,4,5,6,7-heptaphenylcyclohepta-1,3,5-triene,[3] the monobromide,[3] tribromide,[3] triiodide,[4] fluoroborate,[3] and potassium[4] salts of the 1,2,3,4,5,6,7-heptaphenyltropylium ion, and several 7,8,9,10,11-pentaphenylcyclohept[*a*]acenaphthylenes and their covalent derivatives.[5] The parent compound **1** was synthesized by Battiste[2] in 1961 via the Diels–Alder reaction of 2,3,4,5-tetraphenylcyclo-2,4-pentadien-1-one (tetracyclone, **2**) and 1,2,3-triphenylcyclopropene (**3**) with the subsequent loss of carbon monoxide from the initially formed Diels–Alder adduct. By varying[2] the reaction conditions (temperature and solvent) the product **1** could be



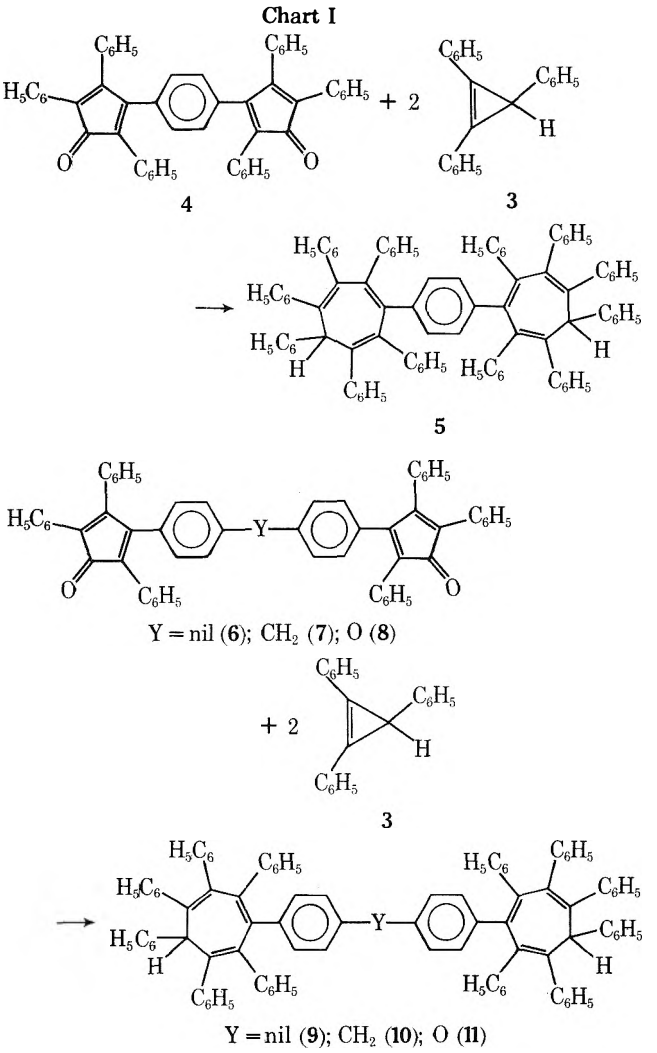
obtained directly. The only report[4] of a bis(heptaphenylcycloheptatriene) as a possible was product in the zinc reduction of the heptaphenyltropylium salts, but none of the bis analogue was isolated.

We now wish to report the successful synthesis of several bis(heptaphenylcycloheptatrienes) and their electronic and unique thermal behavior.

Synthesis. The route chosen to prepare the bis(heptaphenylcycloheptatrienes) was via the Diels–Alder reaction of the dienophile **3** with several bistetracyclone[6,7] dienes (Chart I). Reaction of a 1:2 ratio of diene to dienophile in refluxing diglyme for periods ranging from 14 to 19 days afforded the bis(heptaphenylcycloheptatrienes) in yields ranging from 51 to 87% (Table I).

Electronic Spectra. The spectra features for the bis(heptaphenylcycloheptatrienes) in 1,2-dichloroethane are shown in Table II and consist of a major band in the region 2600–2680 Å and a shoulder in the region 2750–3200 Å. The

Chart I



molar extinction coefficients at the wavelength of maximum absorption for compounds **5**, **9**, **10**, and **11** are all approximately double that for the parent molecule **1**, which indicates that the major chromophore in the bis(heptaphenylcycloheptatrienes) is an individual heptaphenylcycloheptatriene unit.

Thermal Behavior. In obtaining the melting point for the parent 1,2,3,4,5,6,7-heptaphenylcyclohepta-1,3,5-triene (**1**), it is clearly observed that the solid becomes a liquid in the range 289–290 °C. However, when the same technique was used to obtain the melting points for compounds **5**, **9**, **10**, and **11**, no true melting points were observed; instead, at the temperatures reported in Table III, the solids gave the appearance of softening (sintering) but no liquefaction occurred.

Table I. Physical Data for Bis(heptaphenylcycloheptatrienes)

Compd	Reaction time, days	Yield, %	Formula[a]
1,4-Bis(2,3,4,5,6,7-hexaphenylcycloheptatri-1,3,6-enyl)benzene (5)	14	77	$C_{92}H_{66}$
4,4′-Bis(2,3,4,5,6,7-hexaphenylcycloheptatri-1,3,6-enyl)biphenyl (9)	16	51	$C_{98}H_{70}$
4,4′-Bis(2,3,4,5,6,7-hexaphenylcycloheptatri-1,3,6-enyl)diphenylmethane (10)	14	79	$C_{99}H_{72}$
4,4′-Bis(2,3,4,5,6,7-hexaphenylcycloheptatri-1,3,6-enyl)diphenyl ether (11)	19	87	$C_{98}H_{70}O$

[a] Satisfactory analytical data (±0.3% for C, H) for all compounds were submitted for review.

To further investigate this observation differential thermal analysis (DTA) was performed on the bis(heptaphenylcycloheptatrienes) and, although no endotherm or exotherm was observed in the thermograms which would correspond to the visually observed point of softening, each of the thermograms did show two or three endotherms (Table III). This particular type of thermal behavior could be attributed to several phenomena: decomposition, different crystal forms, thermal cleavage followed by recombination, liquid crystal behavior, or thermal rearrangement. In order to eliminate several of the possibilities proposed above the following experiments were conducted. Samples of compounds **5, 9, 10,** and **11** were all subjected to repetitive DTA determinations on the same samples. After each endotherm was observed, the respective samples were cooled to 25 °C below the temperature of that particular endotherm and the sample was again heated to 25 °C above the temperature of the observed endotherm. This procedure was repeated five times at each endotherm observed for each compound and neither the position of the endotherms nor the ratio of the areas under the endotherms changed for any of the samples. These experiments eliminated the possibility of either decomposition or the presence of different crystals forms, since if either were true, a loss of one or more endotherms or a change in the ratio of the areas under the endotherms should have been observed. A DTA was also performed on a 1:1 mixture of 4,4′-bis(2,3,4,5,6,7-hexaphenylcycloheptatri-1,3,6-enyl)diphenylmethane (**10**) and 4,4′-bis(2,3,4,5,6,7-hexaphenylcycloheptatri-1,3,6-enyl)diphenyl ether (**11**) to establish if the thermal behavior of the original samples was due to thermal cleavage followed by recombination. If this process was indeed occurring then the thermogram of the original mixture should reveal the original five endotherms at 431, 435, 563, 570, and 656 °C corresponding to the original two compounds, whereas subsequent thermograms should reveal other endotherms corresponding to the newly formed recombination products. Again five repetitive DTA's on the same sample mixture over the entire temperature range did not show any new endotherms or any change in the ratio of the areas under the originally observed endotherms.

The remaining possibility to explain the thermal behavior of the bis(heptaphenylcycloheptatrienes) is liquid crystal behavior which can be determined by observing the birefringence of compounds **5, 9, 10,** and **11** with the aid of a polarizing microscope fitted with a hot stage. Owing to the specialized nature of the equipment required for these determinations it was not possible for us to establish this possibility; however, the liquid crystal explanation is the most viable explanation available to explain the observed thermal behavior of these compounds.

Thermal Behavior of 1,2,3,4,5,6,7-Heptaphenylcyclohepta-1,3,5-triene (1). Although compound 1 does show a true melting point in the range 289–290 °C, repetitive DTA's were performed on a single sample of this compound in order to use the results obtained as a model for the thermal behavior of the bis(heptaphenylcycloheptatrienes). Surprisingly the first five repetitive DTA's performed showed the position of the observed endotherm to be lower than the preceding DTA, while the endotherms obtained from runs 5 and 6 were constant (Table IV). At this point a new sample of 1 was placed in a Carius tube, sealed under an inert atmosphere of nitrogen, and placed in a Wood's metal bath at 300 °C for 45 min. After this time the sample was removed and its melting point taken and compared with the melting point of an unheated sample. The melting point of the heated sample was 238–240 °C, while the melting point of the unheated sample was 289–290 °C. Both the infrared and the NMR spectra of the heated sample were taken and compared to the corresponding spectra taken

Table II. Spectral Features of Heptaphenylcycloheptatriene and Bis(heptaphenylcycloheptatrienes)

Registry no.	Compd[a]	λ_1, Å	$\epsilon_1 \times 10^{-3}$	Point of inflection, Å	λ_{sh}, Å	$\epsilon_2 \times 10^{-3}$
1835-56-9	1,2,3,4,5,6,7-Heptaphenylcyclohepta-1,3,5-triene (1)[b]	2675	27.8	3000	3120	14.8
59907-73-2	1,4-Bis(2,3,4,5,6,7-hexaphenylcycloheptatri-1,3,6-enyl)benzene (5)	2680	57.5	2680	2755	50.2
59907-74-3	4,4′-Bis(2,3,4,5,6,7-hexaphenylcycloheptatri-1,3,6-enyl)biphenyl (9)	2680	60.9	2845	3200	37.2
59907-75-4	4,4′-Bis(2,3,4,5,6,7-hexaphenylcycloheptatri-1,3,6-enyl)diphenylmethane (10)	2650	60.3	2990	3190	28.6
59907-76-5	4,4′-Bis(2,3,4,5,6,7-hexaphenylcycloheptatri-1,3,6-enyl)diphenyl ether (11)	2680	61.6	2980	3190	31.9

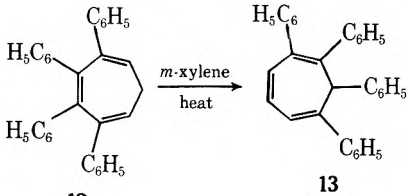
[a] 1,2-Dichloroethane used as solvent. [b] Reported[2] $\lambda_{max}(CH_3CN)$ (log ϵ) 2660 (4.46), 3060 (sh) (4.19).

Table III. Differential Thermal Analysis of Bis(heptaphenylcycloheptatrienes)

Compd	Observed sintering point, °C	Endotherms, °C
5	190	445 and 662
9	218–220	440 and 644
10	185	431, 563, and 656
11	302–305	435 and 570

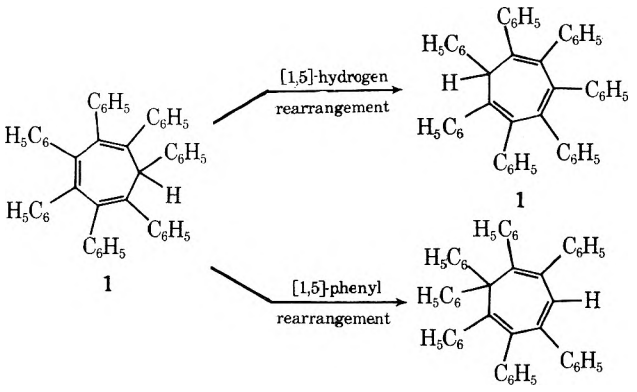
on an unheated sample and several differences were observed. The infrared spectrum of the heated sample was similar to the infrared spectrum of the unheated sample except for the disappearance of four peaks at 1574 (saturated C–H out-of-plane bending or wagging in a cycloalkane), 1328, 1308, and 730 cm^{-1}. The NMR spectrum of the heated sample lacked the singlet at τ 4.73 which was present in the sample before heating and which has been attributed to the cyclic proton on C_7,[8] while the mass spectrum of the sample after heating showed the same molecular weight as the mass spectrum for the unheated sample.

The above results strongly indicate that the sample after heating differs from an unheated sample only to the extent of the positioning of one proton, which appears to be explainable in terms of a thermally allowed[9] [1,5]-phenyl rearrangement. It has been reported[10] that heating 2,3,4,5-tetraphenylcyclohepta-1,3,5-triene (12) in *m*-xylene affords



12 13

1,2,6,7-tetraphenylcyclohepta-1,3,5-triene (13) via a thermal [1,5]-hydrogen rearrangement. However, if 1,2,3,4,5,6,7-heptaphenylcyclohepta-1,3,5-triene (1) underwent a similar thermal [1,5]-hydrogen rearrangement the product formed would be identical in structure with the starting material and no change in the spectra or melting point should be observed. The observed spectral and melting point changes can be explained, however, if compound 1 undergoes a thermal [1,5]-phenyl rearrangement upon heating.



1 1

Experimental Section

General. The melting points of all compounds melting below 250 °C were taken on a Thomas-Hoover oil bath melting point apparatus and are corrected; melting points above 250 °C were taken on a Mel-Temp capillary melting point apparatus and are also corrected. A Stone thermal analyzer was used to obtain the differential thermal analysis (DTA) information. Infrared spectra were taken on solid potassium bromide pellets using a Perkin-Elmer IR-621 grating spectrophotometer and the ultraviolet spectra were recorded on a Cary 14 recording spectrophotometer using a set of matched 1.0-cm quartz cells. Duplicate samples were run for each ultraviolet spectrum reported and all spectral values obtained agreed to within ±0.01% for the wavelength determinations and ±1.00% for the molar extinction coefficient determinations. Ultraviolet spectra were taken in freshly distilled 1,2-dichloroethane with the samples being weighed on a microbalance. No solubility problems were encountered. Mass spectra were obtained on a Hitachi Perkin-Elmer RMV-6E mass spectrometer at 50 eV.

Table IV. Repetitive Differential Thermal Analysis of a Single Sample of Heptaphenylcycloheptatriene

Run no.	Endotherm, °C	Run no.	Endotherm, °C
1	289	4	259
2	284	5	240
3	264	6	240

1,2,3-Triphenylcyclopropene (3). This compound was prepared in an overall yield of 45% via the 1,2,3-triphenylcyclopropenyl *tert*-butyl ether[11] followed immediately by reduction using triethylsilane.[12]

Bistetracyclones (4, 6, 7, and 8). The bistetracyclones were all prepared via literature procedures.[6,7]

Bis(heptaphenylcycloheptatrienes) (5, 9, 10, and 11). The following general procedure was used for the preparation of all the bis(heptaphenylcycloheptatrienes). Into a 500-ml, round-bottomed flask equipped with a reflux condenser and a magnetic stirrer were placed 10 mmol of the appropriate bistetracyclone and 30 mmol of 1,2,3-triphenylcyclopropene (3) in 250 ml of diglyme. The reaction mixture was refluxed for the appropriate number of days reported in Table I, then the diglyme was removed by vacuum distillation. To the remaining solution was added 500 ml of 95% ethanol and the solid which separated was collected and dried. Recrystallization from a 1:5 benzene–ethanol solution afforded analytically pure samples in the yields reported in Table I. Other solvents used for this reaction included benzene, toluene, *p*-xylene, and methyl isobutyl ketone, but these solvents all gave lower yields than those obtained with diglyme.

Thermal Analysis of Bis(heptaphenylcycloheptatrienes). Differential thermal analyses (DTA) were performed on analytical samples of all the bis(heptaphenylcycloheptatrienes) under an inert atmosphere of dry nitrogen. After each endotherm was obtained the instrument was cooled to 25 °C below the temperature of that particular endotherm and the sample was again heated to 25 °C above the temperature of the observed endotherm. This procedure was repeated five times for each endotherm observed and for each compound. No change in position or ratio of areas of the endotherms was observed in any experiment.

A 1:1 mixture of 10 and 11 was prepared by grinding the samples together in a mortar and pestle and subjected to the above procedure and no change in positions or ratio of areas of the endotherms was observed.

Thermal Analysis of Heptaphenylcycloheptatriene (1). A differential thermal analysis was performed on an analytical sample of 1 under an inert atmosphere of nitrogen. After the entire thermogram was obtained the instrument was cooled to room temperature and the same sample was rescanned from room temperature to 500 °C. This procedure was repeated six times and the results are shown in Table IV.

A 0.5-g sample of 1, mp 289–290 °C, was placed in a Carius tube, and the tube sealed under nitrogen and placed in a Wood's metal bath at 300 °C for 45 min. After this time the tube was removed, cooled, and opened, and the yellow solid removed and recrystallized from a 1:4 mixture of benzene–ethanol. The melting point of the sample obtained was 238–240 °C.

Unheated 1: ir (KBr) 3082, 3060, 3023, 1945, 1875, 1800, 1743, 1598, 1574, 1493, 1488, 1442, 1438 (sh), 1328, 1308, 1156, 1090, 1080 (sh), 1070, 1040, 1028, 1023 (sh), 1002, 917 (sh), 910, 845, 804, 788, 768, 734, 730, 703, 588, 580 (sh), 578, and 540 cm^{-1}; NMR ($CDCl_3$) τ 2.03–3.70 (m, 35, ArH) and 4.73 (s, 1, cyclic proton) [lit.[8] 2.10–3.85 (m, ArH) and 4.73 (s)].

Heated 1: the ir (KBr) spectrum of 1 after heating was the same as the spectrum of 1 obtained before heating except for peaks at 1574, 1328, 1308, and 730 cm^{-1}, which were absent; NMR ($CDCl_3$) τ 2.10–3.85 (m, ArH), no signal observed at 4.73.

The mass spectra of both the heated and the unheated samples were essentially identical. The sample after heating was scanned to *m/e* 1600 and no peak corresponding to a dimer of 1 was observed. The C and H analyses for both the heated and unheated samples were satisfactory.

Registry No.—**2**, 479-33-4; **3**, 16510-49-9; **4**, 3432-73-3; **6**, 16325-29-4; **7**, 59907-77-6; **8**, 13092-45-0.

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On the Photochemistry of Hexamethyl-2,4-cyclohexadienone 4,5-Epoxide and on Subsequent Rearrangements of Its Photoisomer, *endo*-5-Acetyl-1,3,3,4,5-pentamethylbicyclo[2.1.0]pentan-2-one

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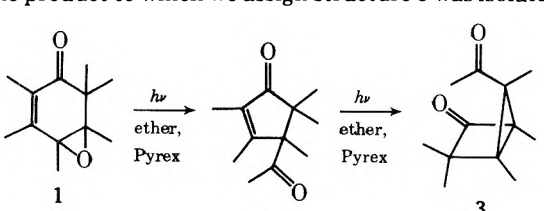
Irradiation (Pyrex) of hexamethyl-2,4-cyclohexadienone 4,5-epoxide (1) gives 2,3,4,5,5-pentamethyl-4-acetyl-2-cyclopentenone (2), which then photoisomerizes to *endo*-5-acetyl-1,3,3,4,5-pentamethylbicyclo[2.1.0]pentan-2-one (3). This bicyclic diketone is photochemically and thermally labile. On irradiation in ether through Corex, 3 is converted to lactones 4 and 5. The thermal rearrangements of 3, which probably proceed via ketene 7, show a remarkable solvent effect. In carbon tetrachloride the products are 2 and lactone 8, whereas in methanol the products are lactones 9 and 10. Mechanisms for all these transformations are proposed and supported by deuterium labeling experiments.

Although the photochemistry of α,β-epoxy ketones has been extensively studied,[1] only recently have the vinylogous α,β-unsaturated γ,δ-epoxy ketones received attention.[2-6] The few results reported thus far suggest that this class of epoxy ketones undergoes a wide range of fascinating photochemical rearrangements.

One class of easily accessible[7] α,β-unsaturated γ,δ-epoxy ketones whose photochemistry has not been studied are the 2,4-cyclohexadienone 4,5-epoxides. In this paper we describe the irradiation of hexamethyl-2,4-cyclohexadienone 4,5-epoxide (1).[8] The initial photoproduct undergoes further photoisomerization to a second product which itself is both photo- and thermolabile, resulting in an interesting array of molecular rearrangements.

Results and Discussion

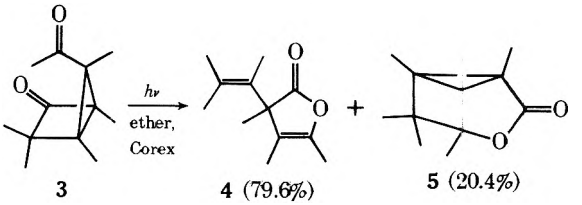
Photochemistry of 1. Irradiation of 1 (0.01 M in ether, 0 °C) through Pyrex was followed by NMR. As peaks due to 1 decreased in intensity, a new set of peaks which could be ascribed to the known 2[8] appeared. At 50% conversion both sets of peaks began to diminish in area in favor of a third set of peaks. After 16 h only the third set was present, and a crystalline product to which we assign structure 3 was isolated in



1 2 3

90% yield.[9] The structural assignment is based on spectra and on chemical transformations. Ir bands at 1760 and 1710 cm^{-1} are attributed to the cyclobutanone and acetyl absorptions, respectively. The absence of ir bands in the 1500–1680-cm^{-1} region together with the fact that all the methyl signals in the NMR spectrum (except the acetyl methyl, at δ 2.15) appeared as singlets above δ 1.3 indicated the absence of C=C bonds. The mass spectrum showed that 3 was an isomer of 1 and 2 (M^+ 194, 20%); the base peak at *m/e* 152 corresponded to loss of ketene (presumably from the acetyl group). The endo configuration for the acetyl group is required by subsequent reactions of 3 (vide infra).

Photochemistry of 3. The bicyclic diketone 3 had a λ_{max} (MeOH) at 225 nm (ϵ 2590) and was photolabile when irradiated through a Corex filter (0.017 M in ether, 0 °C). The major photoproduct was assigned structure 4, and the minor product is tentatively assigned structure 5. The $\nu_{C=O}$ at 1790 cm^{-1} in 4 is consistent with the five-membered enol lactone



3 4 (79.6%) 5 (20.4%)

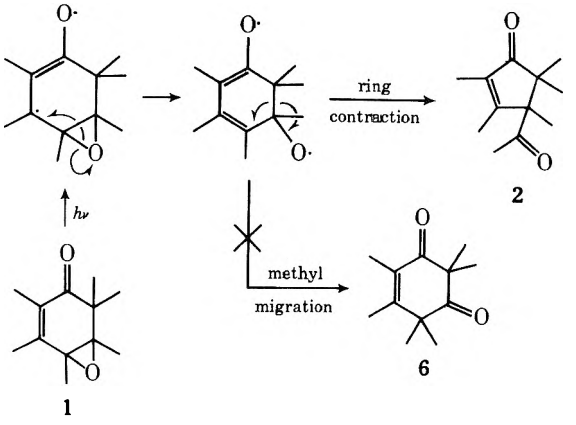
moiety. The NMR spectrum of 4 showed two homoallylically coupled methyl signals at δ 1.50 and 1.87 assigned (from labeling experiments; vide infra) to the allylic methyls of the lactone ring. Other allylic methyl signals appeared at δ 1.70 (6 H) and 1.37 (3 H),[10] and the aliphatic methyl was a sharp singlet at δ 1.30.

The minor product 5 had a $\nu_{C=O}$ at 1760 cm^{-1} consistent with a strained five-membered lactone. The absence of ir bands in the 1500–1680-cm^{-1} region and the location of all methyl singlets in the NMR spectrum at or above δ 1.20 showed the absence of C=C bonds. The mass spectrum of 5

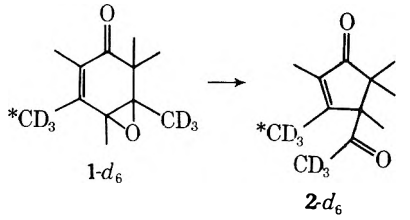
showed a small M^+ peak at *m/e* 194 (2%) and a base peak at *m/e* 135 corresponding to the loss of $CO_2 + CH_3$.[11]

Photochemical Mechanisms and Labeling Results. The photoisomerization of **1** to **2** proceeds according to Scheme I.[12]

Scheme I



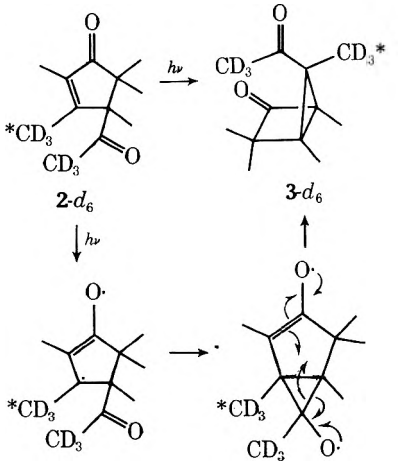
Following excitation and C_γ–O bond cleavage[2,3] a 1,2-alkyl shift occurs. Preferred ring contraction (to give **2**) over methyl migration (to give **6**) is consistent with the usual migratory aptitudes observed in the photorearrangement of α,β-epoxy ketones to β-diketones.[1,13] Consistent with this scheme, irradiation of labeled **1**[8] (samples of **1**-d_3, labeled in both the C-3 and C-5 methyl groups, and of **1***, labeled only in the C-3 or asterisked methyl group, were irradiated) gave labeled **2** as shown (the NMR spectrum of **2** is such that the location of the label was readily apparent).



1-d_6 **2**-d_6

The photoisomerization of **2** to **3** can be regarded as an oxa-di-π-methane rearrangement.[14] The reaction is stereoselective; only the endo-acetyl isomer is formed. Similar photoisomerizations of 4-acyl-2-cyclopentenones have been reported.[15,16] Consistent with this 1,2-acyl shift mechanism, we find the label results in Scheme II. The acetyl methyl label

Scheme II

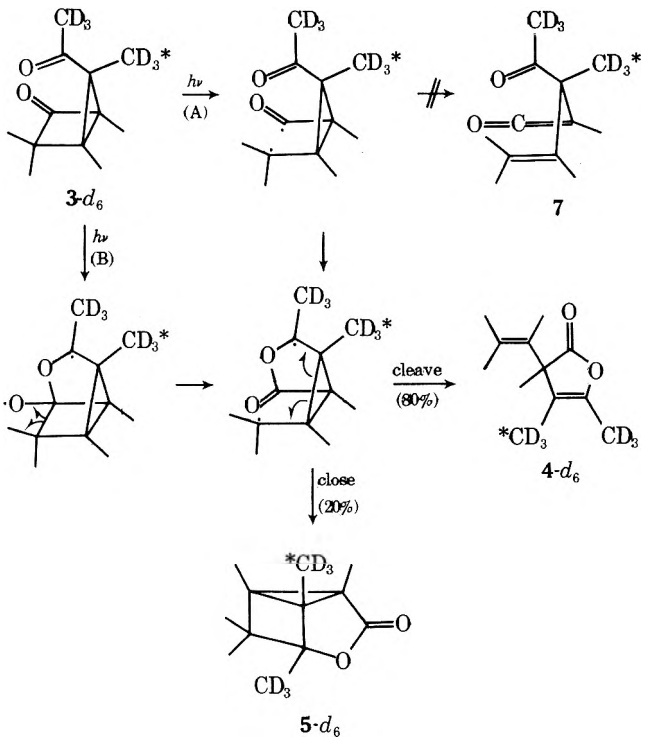


2-d_6 **3**-d_6

in **2**-d_6 became the acetyl methyl in **3**-d_6. On irradiation of **2***, the peak which disappeared from the spectrum of the resulting **3*** was the peak at δ 1.23. Although there is no a priori way of assigning this signal from chemical shifts, we can confidently assign it (i.e., the CD_3* group in **3**) to the C-5 methyl position as shown because of the label location in the products of subsequent photochemical and thermal rearrangements of **3** (vide infra).

Plausible mechanisms for the photoisomerization of **3** to **4** and **5** are shown in Scheme III. The formation of lactones

Scheme III

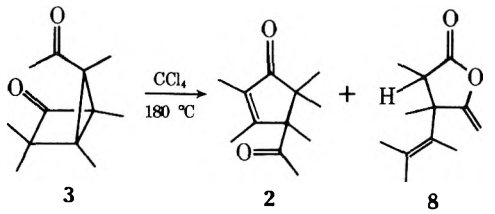


3-d_6 **7** **4**-d_6 **5**-d_6

4 and **5** requires the endo geometry for the acetyl group in **3**. Two paths (A and B) are possible. Path A begins with Norrish type I cleavage of the cyclobutanone ring, followed by lactonization to give a 1,4 diradical that can either cleave to give **4** or close to give **5**. A possible flaw in this route is that the first formed diradical might be expected to cleave to give the ketene **7**. Indeed the conversion of **3** → **7** does occur thermally (vide infra), but is not observed photochemically. Consequently we propose path B as perhaps a better alternative for the photoisomerization mechanism of **3**. Both paths lead to the same diradical, but path B avoids an intermediate which could give ketene **7**. The labeling consequences of both paths are identical; the paths differ only in the timing of events.

Irradiation of **3**-d_6 gave **4**-d_6 lacking methyl signals at δ 1.50 and 1.87. Irradiation of **3*** gave **4*** lacking the methyl signal at δ 1.50 and with the quartet at δ 1.87 (homoallylic coupling, J = 1 Hz) sharpened to a singlet. Consequently the two labeled methyl groups in **4**-d_6 must be adjacent to one another, as shown in the structure and predicted from the mechanism in Scheme III. It is reasonable that of the two labeled methyl groups, the one at lower field (δ 1.87) is adjacent to the lactone oxygen atom.

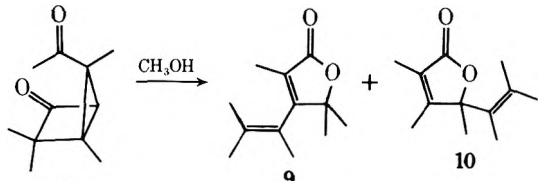
Thermal Rearrangements of 3. Diketone **3** was thermally labile. At room temperature the ir spectrum showed, in addition to the carbonyl bands at 1760 and 1710 cm^{-1}, a well-defined band at 2300 cm^{-1} attributable to a ketene. The relative intensities of these bands remained constant with time, suggesting an equilibrium between **3** and the ketene. Gradually, however, both sets of peaks decreased in intensity and were replaced with a new set of peaks characteristic of **2**. Indeed, when **3** was stored for several weeks at −15 °C in the solid state it slowly reverted to **2**. When **3** was heated in CCl_4 solution at 180 °C (sealed tube) it was converted mainly to **2**, though a minor product to which we assign structure **8** was also



3 2 8

formed. The mass spectrum of **8** (M^+ *m/e* 194, 32%) showed it to be an isomer of **3**. The $\nu_{C=O}$ at 1795 cm^{-1} was characteristic of an enol lactone. The NMR spectrum showed two vinyl protons (δ 4.07, 4.53), and a mutually coupled methyl doublet at δ 1.02 and methine quartet at δ 2.38, the latter having a chemical shift consistent with location α to the carbonyl group. In addition there was a sharp methyl singlet at δ 1.50 and peaks due to the allylic methyls at δ 1.60 (6 H) and 1.70 (3 H).

Believing ketene **7** to be an intermediate in the conversion of **3** to **2** and **8**, and hoping to trap the ketene, we treated **3** with a few drops of methanol at room temperature. Under these conditions **3** rearranged to two new isomers **9** and **10** (in the



3 9 10

ratio 1:3). Each product had a $\nu_{C=O}$ at 1745 cm^{-1} consistent with a Δ^1-butenolide structure. Compound **9** had λ_{max} (MeOH) at 223 nm (ε 2600) and 255 (1070) consistent with the extended conjugated system, whereas **10** had a normal Δ^1-butenolide spectrum, λ_{max} (MeOH) 230 nm (ε 3100). The NMR spectrum of **9** showed a 6 H singlet at δ 1.40 for the *gem*-dimethyl group, and two 6 H multiplets at δ 1.60 and 1.77 for the four allylic methyl groups. Shift reagent showed that one of the peaks at δ 1.60 was due to the methyl α to the carbonyl group. The NMR spectrum of **10** showed only one aliphatic methyl singlet (δ 1.53) and five allylic methyls, as multiplets at δ 1.62 (6 H) and 1.72 (6 H) and a quartet at δ 1.82 due to the C-3 methyl (shown by deuterium labeling to be coupled to the C-2 methyl at δ 1.72).

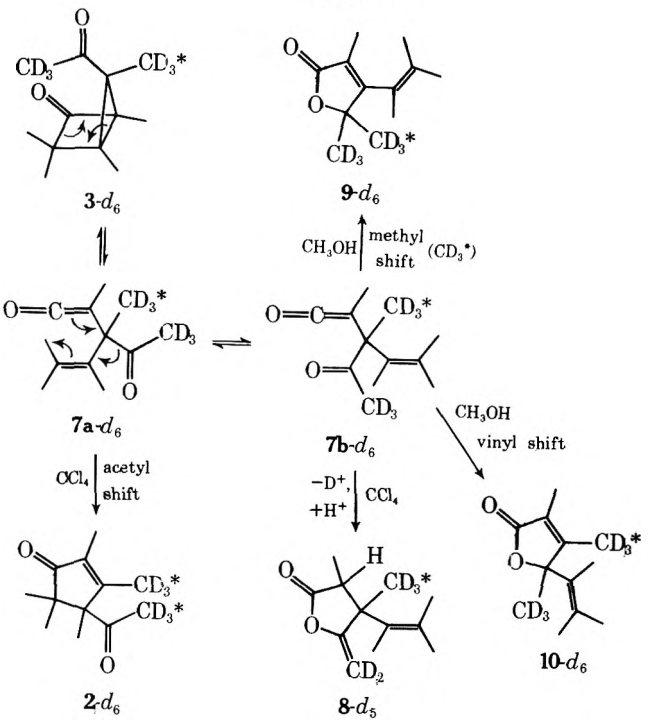
Mechanism of the Thermal Rearrangements of 3, and Supporting Labeling Experiments. We believe that all of the thermal rearrangement products of **3** (i.e., **2, 8, 9** and **10**) are derived from ketene **7** as shown in Scheme IV. Cyclization of the ketene in conformation **7a,** accompanied by a 1,2-acetyl shift as indicated by the arrows, can give **2**. Cyclization from conformation **7b** gives the three lactones. This can occur without any group migrations but with proton loss from the acetyl methyl group to give **8**, or with rearrangement of a methyl or vinyl group to give **9** and **10**, respectively.

We have no explanation for the dramatic solvent effects on these reactions. The inability of methanol to trap ketene **7** is not surprising, however, since hindered ketenes often are inert toward this relatively weak nucleophile.[17]

As indicated in Scheme IV, the proposed mechanisms imply certain labeling consequences, and these were verified experimentally. Rearrangement of **3*** in carbon tetrachloride gave **2*** in which the peak at δ 1.95 diminished in area from 6 H to 3 H, and that at δ 1.75 (due to the C-2 methyl) sharpened to a singlet. From **3**-d_6, the resulting **2**-d_6 lacked entirely the six-proton δ 1.95 peak due to the C-3 and acetyl methyls. In the same experiments, the resulting **8*** lost the sharp aliphatic methyl singlet at δ 1.50 and the **8**-d_5 lost the vinyl signals at δ 4.07 and 4.53 as well.

Rearrangement of **3*** in methanol gave **9*** in which the signal δ 1.40 due to the *gem*-dimethyl group decreased in area

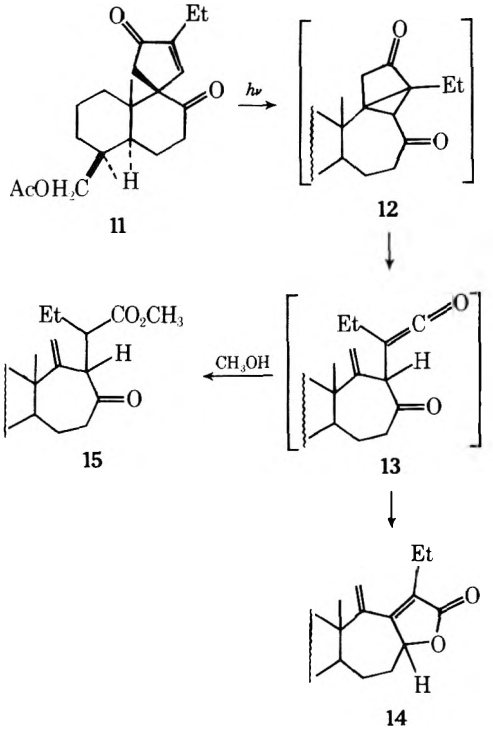
Scheme IV



from 6 H to 3 H; starting with **3**-d_6 this peak in **9**-d_6 disappeared entirely. In the same experiments, the resulting **10*** lacked the quartet at δ 1.82 and the peak at δ 1.72 sharpened to a singlet; in addition to these changes, the resulting **10**-d_6 also lacked the singlet at δ 1.53.

All the labeling results are consistent with the mechanism in Scheme IV.

Some thermal rearrangements similar to those of **15** have been reported,[15,16,18] and in some cases[18] the intermediate ketene can be trapped with methanol. For example, the irradiation of **11** gave the butenolide **14**,[18] presumably via dike-



11 12 15 13 14

tone **12** which then thermally rearranged to ketene **13.** When the irradiation of **11** was run in methanol, the product was **15.**

In summary, through photochemical or thermal rear-

rangements we have converted the epoxy ketone **1** to a rather wide array of structural isomers (**2**, **3**, **4**, **5**, **8**, **9**, and **10**) and have established plausible mechanisms for these rearrangements. We are continuing to investigate structural effects on these rearrangements.

Experimental Section[19]

Irradiation of 4,5-Epoxy-2,3,4,5,6,6-hexamethyl-2,4-cyclohexadienone (1). A degassed solution of **1**[8] (50 mg, 0.26 mmol) in 25 ml of anhydrous ether was irradiated through Pyrex at 0 °C with a 450-W Hanovia Type L lamp. The reaction was followed by NMR. Signals due to **1** decreased in intensity as new peaks due to **2**[8] appeared. Gradually both sets of peaks were replaced by a new set due to **3**; the conversion of **1** to **3** required 16 h. Evaporation of the ether and recrystallization from petroleum ether (bp 30–60 °C) gave 5-acetyl-1,3,3,4,5-pentamethylbicyclo[2.1.0]pentan-2-one (**3**) as a white solid (45 mg, 90%, decomposed on heating): ir (CCl_4) 3000 (m), 1760 (s), 1710 (s), 1470 (w), 1400 (w), 1370 (w), 1230 cm^{-1} (w); uv (MeOH) λ_{max} 225 nm (ϵ 2590); NMR (CCl_4) δ 0.77 (s, 3 H, C-3 methyl), 1.07 (s, 3 H, C-3 methyl), 1.18 (s, 3 H), 1.23 (s, 3 H, C-5 methyl), 1.27 (s, 3 H), 2.15 (s, 3 H, acetyl methyl); mass spectrum (70 eV) *m/e* (rel intensity) 195 (3), 194 (20), 179 (9), 153 (13), 152 (100), 151 (31), 150 (9), 137 (56), 123 (48), 108 (54), 93 (28), 91 (18), 81 (34), 79 (13). Owing to the thermal instability of **3**, no attempt was made to obtain an elemental analysis.

Irradiation of Labeled 1. The irradiation and workup conditions were as described for the unlabeled epoxy ketone. From 4,5-epoxy-3-trideuteriomethyl-2,4,5,6,6-pentamethyl-2,4-cyclohexadienone (**1***) the resulting **2*** had an NMR spectrum identical with that of unlabeled **2**[8] except that the signal at δ 1.95 (C-3 and acetyl methyls) was reduced in area from 6 H to 3 H and the quartet at δ 1.75 (C-2 methyl) sharpened to a singlet. The **3*** obtained from further irradiation had an NMR spectrum identical with that of unlabeled **3** except that the singlet at δ 1.23 (C-5 methyl) was absent.

From 4,5-epoxy-3,5-bis(trideuteriomethyl)-2,4,6,6-tetramethyl-2,4-cyclohexadienone (**1**-d_6), the resulting **2**-d_6 had an NMR spectrum identical with that of **2*** except that the signal at δ 1.95 (C-3 and acetyl methyls) was entirely absent. The **3**-d_6 obtained from further irradiation had an NMR spectrum identical with that of **3*** except that the signal at δ 2.15 (acetyl methyl) was absent.

Irradiation of 5-Acetyl-1,3,3,4,5-pentamethylbicyclo[2.1.0]pentan-2-one (3). A degassed solution of 100 mg (0.52 mmol) of **3** in 30 ml of anhydrous ether was irradiated through Corex with a 450-W Hanovia lamp at 0 °C. The photolysis was followed by NMR, and was complete in about 12 h. Analytical VPC (5 ft × 0.125 in. column, 10% FFAP on Chromosorb W, AW-DMCS 80/100, 165 °C) showed two components: **4** (79.6%, retention time 5 min) and **5** (20.4%, 7 min). Preparative VPC (5 ft × 0.25 in. column, 10% FFAP on Chromosorb W, 80/100, 145 °C) gave the pure lactones.

For **4**: ir (CCl_4) 2960 (w), 2910 (m), 2850 (w), 1790 (s), 1700 (w), 1450 (m), 1385 (m), 1370 (w), 1365 (w), 1290 (w), 1275 (w) 1225 (m), 1030 (s), 980 (m), 930 cm^{-1} (w); uv (EtOH) only end absorption; NMR (CCl_4), see footnote 20; the peaks at δ 1.50 and 1.87 were quartets, J = 1 Hz; mass spectrum (70 eV) *m/e* (rel intensity) 194 (13), 179 (6), 151 (100), 126 (21), 123 (35), 81 (26), 67 (14), 55 (15), 53 (19).

A microanalysis was done on a hexadeuterio sample of this lactone (**4**-d_6). Anal. Calcd for $C_{12}H_{12}D_6O_2$: C, 71.94. Found: C, 72.00.

For lactone **5**: mp 104–106 °C; ir (CCl_4) 2950 (m), 2920 (m), 2850 (m), 1760 (s), 1460 (w), 1380 (m), 1300 (m), 1050 (m), 950 cm^{-1} (m); uv (EtOH) λ_{max} 220 nm (ϵ 890); NMR (CCl_4) δ 0.70 (s, 3 H), 1.03 (s, 3 H), 1.12 (s, 6 H), 1.17 (s, 3 H), 1.20 (s, 3 H); mass spectrum (70 eV) *m/e* (rel intensity) 194 (2), 179 (2), 155 (55), 135 (100), 120 (16), 119 (42), 107 (19), 104 (22), 93 (21), 91 (27), 44 (60), 43 (25), 41 (24), 39 (20).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.22; H, 9.36.

Irradiation of Labeled 3. The conditions and workup procedure were as for the unlabeled material. From **3*** the resulting **4*** had an NMR spectrum identical with that of **4** except that the signal at δ 1.50 was absent and the peak at δ 1.87 sharpened to a singlet. The spectrum of the resulting **5*** was identical with that of **5** except that the singlet at δ 1.17 was absent.

From **3**-d_6 the resulting **4**-d_6 had an NMR spectrum identical with that of **4** except that the signals at δ 1.50 and 1.87 were absent. The NMR spectrum of the resulting **5**-d_6 was identical with that of **5** except that the singlets at δ 1.17 and 1.20 were absent.

Thermal Rearrangement of 3 in CCl_4. When **3** (40 mg, 0.21 mmol) in 0.5 ml of CCl_4 was heated in a sealed tube at 180 °C for 3 h it was converted to a mixture of **2**[8] and **8** (ca. 9:1 by NMR). Preparative VPC (5 ft × 0.25 in. column, 10% FFAP on Chromosorb W, 80–100 mesh, 160 °C) gave diketone **2** (retention time 45 min) and lactone **8** (retention time 35 min). For lactone **8**: ir (CCl_4) 2950 (w), 1795 (s), 1695 (w), 1660 (m), 1460 (m), 1390 (w), 1250 (w), 1200 (w), 1130 (w), 1080 (w), 1050 (m), 990 (w), 860 cm^{-1} (w); uv (MeOH) λ_{max} 225 nm (ϵ 1310); NMR (CCl_4) see footnote 20; the peaks at δ 1.02 and 2.38 were a doublet and a quartet, respectively, J = 7 Hz, the peaks at δ 4.07 and 4.53 were doublets, J = 2 Hz, and the peak at δ 1.60 (6 H) was a multiplet; mass spectrum (70 eV) *m/e* (rel intensity) 194 (32), 179 (32), 152 (23), 151 (100), 137 (29), 136 (15), 133 (25), 123 (13), 121 (10), 109 (20), 107 (10), 91 (14), 81 (12), 79 (12), 77 (14).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.15; H, 9.34.

Thermal Rearrangement of Labeled 3 in CCl_4. The conditions and workup procedure were as described for unlabeled **3**. From **3*** the resulting **2*** had an NMR spectrum identical with that of unlabeled **2**[8] except that the peak at δ 1.95 (C-3 methyl and acetyl methyl) was reduced in area from 6 H to 3 H and the peak at δ 1.75 (C-2 methyl) sharpened to a singlet. The resulting **8*** had an NMR spectrum identical with that of unlabeled **8**[20] except that the singlet at δ 1.50 was absent. From **3**-d_6 the resulting **2**-d_6 had an NMR spectrum identical with that of **2*** except that the signal at δ 1.95 was absent. The resulting **8**-d_5 had an NMR spectrum identical with that of **8*** except that the vinyl proton signals at δ 4.07 and 4.53 were almost entirely absent.

Thermal Rearrangement of 3 in Methanol. When compound **3** was treated with a few drops of methanol, it rearranged to a mixture of lactones **9** and **10** (ca. 1:3 as determined by NMR spectrum). Preparative VPC (5 ft × 0.25 in. column, 10% FFAP on Chromosorb W, 80–100 mesh, 170 °C) gave lactone **9** (retention time 25 min): ir (CCl_4) 2950 (w), 1745 (s), 1700 (m), 1460 (w), 1380 (w), 1280 (m), 1080 (m), 980 cm^{-1} (m); uv (MeOH) λ_{max} 223 nm (ϵ 2600), 255 (1070); NMR (CCl_4) see footnote 20; the peaks at δ 1.60 and 1.77 were multiplets; mass spectrum (70 eV) *m/e* (rel intensity) 195 (11), 194 (78), 179 (14), 151 (20), 136 (23), 123 (12), 109 (36), 108 (78), 107 (14), 93 (100), 91 (28), 77 (25), 65 (13), 53 (20).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.27; H, 9.50.

For lactone **10** (retention time 45 min): ir (CCl_4) 2950 (w), 1745 (s), 1450 (w), 1390 (w), 1330 (w), 1260 (w), 1130 (w), 1090 cm^{-1} (w); uv (MeOH) λ_{max} 230 nm (ϵ 3100); NMR (CCl_4) see footnote 20; the peak at δ 1.82 was a quartet, J = 1 Hz, and the peaks at δ 1.62 and 1.72 were multiplets; mass spectrum (70 eV) *m/e* (rel intensity) 194 (25), 179 (32), 151 (36), 150 (28), 149 (100), 137 (10), 136 (7), 135 (29), 134 (14), 133 (18), 126 (53), 125 (48), 123 (43), 119 (15), 109 (11), 107 (10), 97 (16), 93 (10), 91 (14), 81 (20).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.20; H, 9.47.

Thermal Rearrangement of Labeled 3 in Methanol. The conditions and workup procedure were as with unlabeled material. From **3*** the resulting **9*** had an NMR spectrum identical with that of **9**[20] except that the peak at δ 1.40 was reduced in area from 6 H to 3 H. The resulting **10*** had an NMR spectrum identical with that of **10**[20] except that the signal at δ 1.82 was absent and the multiplet at δ 1.72 sharpened to a singlet. From **3**-d_6 the resulting **9**-d_6 had a spectrum identical with that of **9**[20] except that the 6 H peak at δ 1.40 was absent. The resulting **10**-d_6 had an NMR spectrum identical with that of **10*** except that the singlet at δ 1.53 was absent.

Acknowledgment. We are indebted to the National Institutes of Health (GM 15997) and the National Science Foundation (GP 43659X) for their support of this research.

Registry No.—**1**, 50506-42-8; **1***, 50506-43-9; **1**-d_6, 50506-44-0; **3**, 59873-39-1; **3***, 59873-40-4; **3**-d_6, 59873-41-5; **4**, 59873-42-6; **4**-d_6, 59873-43-7; **5**, 59873-44-8; **8**, 59873-45-9; **9**, 59873-46-0; **10**, 59873-47-1.

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(1) For reviews, see N. R. Bertoniere and G. W. Griffin, *Org. Photochem.*, **3**, 115 (1973); A. Padwa, *ibid.*, **1**, 91 (1967); O. Jeger, K. Schaffner, and H. Wehrli, *Pure Appl. Chem.*, **9**, 555 (1964).
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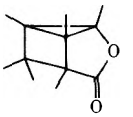
(8) The synthesis and acid-catalyzed rearrangement of **1** has been described: H. Hart, I. Huang, and P. Lavrik, *J. Org. Chem.*, **39**, 999 (1974).
(9) We are indebted to P. Lavrik for initial studies on this system.
(10) The chemical shift of this allylic methyl, which is at a remarkably high field, may be a consequence of shielding by the lactone carbonyl group.
(11) An alternative structure for **5** is



Although this structure seems highly unlikely from a mechanistic viewpoint (see Scheme III), it cannot be conclusively eliminated from the structural data available.
(12) In a future paper we will show that this is not always the only path followed by 2,4-cyclohexadienone 4,5-epoxides and that it depends in part on the substituents attached to the ring.
(13) C. S. Markos and W. H. Reusch, *J. Am. Chem. Soc.*, **89**, 3363 (1967).
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(17) For other examples of ketenes that are not trapped by methanol, see J. Griffiths and H. Hart, *J. Am. Chem. Soc.*, **90**, 3297 (1968), and H. Hart and G. M. Love, *ibid.*, **93**, 6266 (1971).
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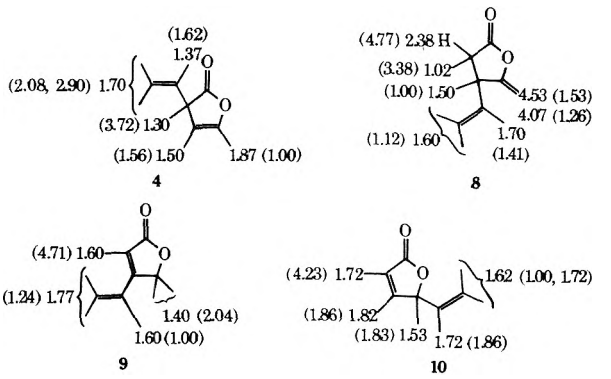
(19) NMR spectra were measured in $CDCl_3$ or CCl_4 solutions using Me_4Si as an internal standard, on a Varian T-60 or HA-100 spectrometer. Ir spectra were recorded on a Perkin-Elmer 237 grating spectrophotometer and were calibrated against a polystyrene film. Uv spectra were obtained on a Unicam SP-800 spectrometer. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6 operated at 70 MeV; we are indebted to Mrs. Ralph Guile for this service. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich.
(20) The NMR assignments for **4**, **8**, **9**, and **10**, are shown below in δ units, with relative downfield shifts in the presence of $Eu(fod)_3$ given in parentheses.



Thermal α-Deoxysilylation of *N,O*-Bis(Trimethylsilyl)-*N*-phenylhydroxylamine

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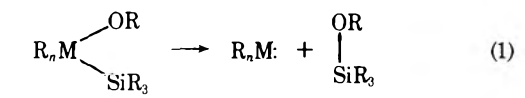
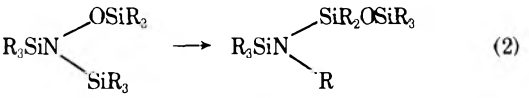
Heating *N,O*-bis(trimethylsilyl)-*N*-phenylhydroxylamine (**4**) at 100 °C in cyclohexene leads to expulsion of hexamethyldisiloxane and formation of mainly aniline (53%), together with a small amount (2%) of 7-phenyl-7-azabicyclo[4.1.0]heptane, and other minor products consistent with the intermediacy of phenylnitrene (PhN̈:). Attempts to trap PhN̈: with stilbenes met with only very limited success; however, thermolysis of **4** in the presence of diethylamine, dibutylamine, and cyclohexylamine gave 85–95% yields of ring-expanded azepine trapping products. The yield of aniline varied (~20–80%) with solvent and was found to generally parallel the H-donating ability of a solvent. Kinetic experiments demonstrated that the thermal fragmentation of **4** is unimolecular and is characterized by $\Delta H^{\ddagger}$ = 27.7 kcal/mol and $\Delta S^{\ddagger}$ = −3.8 eu. The effect of inert solvent variation on the thermolysis rate of **4** is small; a maximal rate acceleration factor of ~6.5 obtains for benzonitrile vs. hexafluorobenzene. A limited amount of comparative thermolysis data was obtained for *O*-methyl-*N*-trimethylsilyl- (**9**) and *O*-methyl-*N*-triethylsilyl-*N*-phenylhydroxylamine (**10**). Various mechanistic aspects relating to the intermediacy of PhN̈: are briefly discussed.

Thermally induced fragmentations of compounds represented by general structure **1** to afford an electron-deficient species and a silyl ether (eq 1) have been reported for cases



1



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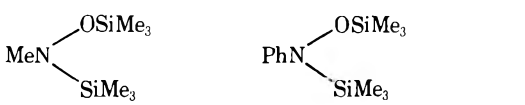
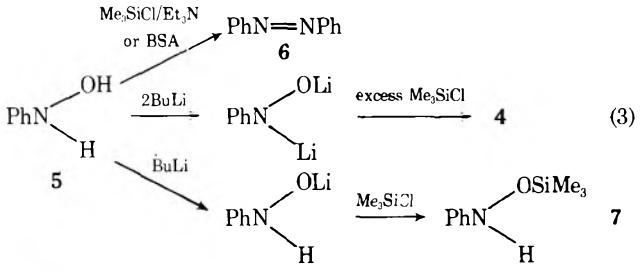


3 **4**

wherein M = C[1] and Si,[2] thus providing a method for carbene (R_2C:) and silylene (R_2Si:) generation, respectively. While such α-deoxysilylation reactions do not apparently obtain for tris(organosilyl)hydroxylamines (**2**), which instead undergo rearrangement according to eq 2,[3] Boudjouk and West[3] were the first to note that hexamethyldisiloxane ($Me_3SiOSiMe_3$) was formed upon heating *N,O*-bis(trimethylsilyl)-*N*-methylhydroxylamine (**3**), and thereby obtained prima facie evidence for the operation of eq 1 in a system having reaction center M = N. We have subsequently reported[4] preliminary observations regarding the thermolytic behavior of analogous silylated hydroxylamine derivatives, and now present details of solvent trapping and kinetic experiments with *N,O*-bis(trimethylsilyl)-*N*-phenylhydroxylamine (**4**), together with ancillary studies of two of its *O*-methyl relatives. Our findings are consistent with unimolecular fragmentation of **4** to afford phenylnitrene (PhN̈:).

Results and Discussion

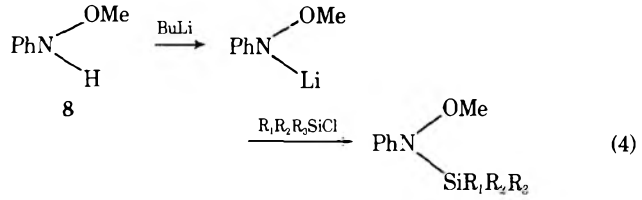
Synthesis. Selection of **4** for the investigation of *N,O*-bis(trimethylsilyl)hydroxylamine systems was based upon the existence of a large body of information[5] regarding PhN̈:, the expected nitrene fragment from α-deoxysilylation of **4**. As shown in eq 3, reaction of *N*-phenylhydroxylamine (**5**) ac-



(3)

cording to the general procedure[6] for bis-silylation of *N*-alkylhydroxylamines with chlorotrimethylsilane (Me_3SiCl) and triethylamine unexpectedly afforded azobenzene (**6**), as did reaction of **5** with *N,O*-bis(trimethylsilyl)acetamide (BSA) under conditions used for hydroxyamines.[7] An optimized yield of **4** (~40%) was, however, eventually obtained by treatment of **5** with 2 equiv of butyllithium (BuLi) at −50 °C and subsequent reaction of the assumed bislithio intermediate with a twofold excess (4 equiv) of Me_3SiCl at temperatures between −50 and −20 °C. Monosilylation of **5** to give *O*-trimethylsilyl-*N*-phenylhydroxylamine (**7**) in ~50% yield was accomplished by means of a similar procedure.

Extension of this approach to tricrganosilylation of *O*-methyl-*N*-phenylhydroxylamine (**8**) was next studied as a means of providing analogues of **4** having graded steric bulk about the silicon bonded to nitrogen (eq 4). Compounds **9** and

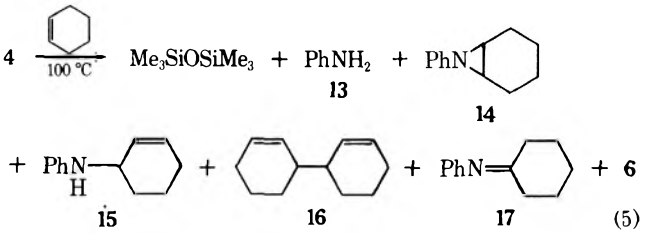


(4)

9, $R_1 = R_2 = R_3 = Me$
10, $R_1 = R_2 = R_3 = Et$
11, $R_1 = R_2 = R_3 = Pr$
12, $R_1 = R_2 = Me$; $R_3 = Ph$

10 were isolated in 4 and 7% yields, respectively; 1,2-anionic rearrangement[8a] of the *N*-lithio intermediate to give $PhN(CH_3)OLi$ and, hence, the corresponding O-silylated isomers of **9** and **10** was not in evidence.[8b] Attempts to prepare **11** and **12** were unsuccessful and led to formation of mainly **6**. These latter failures are attributed to facile coupling of the litho intermediate in eq 4 (see Experimental Section), relative to nucleophilic displacement of chloride ion in the sterically hindered chlorosilanes leading to **11** and **12**. In this connection, it was found that **8** cleanly undergoes decomposition to **6** and 2 equiv of methanol. Kinetic analyses, in which the decrease in [**8**] was followed (VPC) in toluene solution at 40 °C, gave concentration-dependent values for the disappearance rate constant: $2k = 1.46$ (0.20 M), 0.70 (0.10 M), and 0.26×10^{-6} M^{-1} s^{-1} (0.05 M); reaction order $n = 2.04 \pm 0.06$. From a practical standpoint, long-term storage of **8** may be accommodated by use of cooled solutions: e.g., the half-life of 0.2 M **8** is ~6 months at 0 °C. Walter and Schaumann[9] have rationalized the production of **6** from the conjugate base of **8** in terms of PhN̈: intermediacy; however, we have been unable to detect even trace amounts of the expected[5] H-abstraction production, aniline (<1%, VPC), upon decomposition of **8** in toluene at 40 °C.

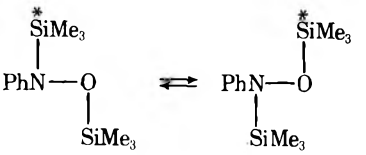
Solvent Trapping Studies for Thermolysis of 4. Isolation of aziridines from reactions of potential arylnitrene generators in the presence of olefins has provided strong support for actual nitrene production;[10,11] consequently, investigation of the thermolysis of **4** in cyclohexene solution was of interest. After 16 h of heating **4** in a 100-fold molar excess of cyclohexene at 100 °C in Pyrex ampules, VPC analyses revealed essentially complete disappearance of **4** with near-quantitative formation of hexamethyldisiloxane ($Me_3SiOSiMe_3$), which is the expected organosilicon fragment from eq 1. Of the eight additional VPC components, four were isolated by preparative techniques and spectroscopically identified as aniline (**13**, 20%), 7-phenyl-7-azabicyclo[4.1.0]heptane (**14**, 2%), secondary amine **15** (4%), and bicyclohexyldiene **16** (22%) (eq 5). Lesser



(5)

amounts (<1%) of *N*-phenylcyclohexylideneimine (**17**) and **6** were characterized by VPC retention time comparisons with authentic samples, and the two remaining trace components (<1%) are yet unidentified. Poor material balance (~25%) was attributed to formation of nonelutable (TLC) dark-colored material. A control experiment, which demonstrated that **14** is thermally stable (120 °C, 14 h) relative to the conditions used for its formation, ruled out the possibility of **15** and/or **17** being produced by decomposition of **14**. Thus, the inherently low yield of **14** parallels the ~5% isolated yield of its 7-ferrocenyl analogue obtained from thermolysis of ferrocenyl azide in cyclohexene.[10]

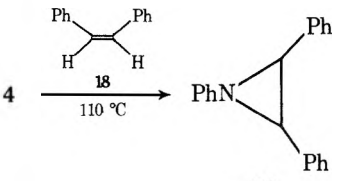
Inasmuch as the formation of products **13**–**17** may be rationalized[5] by the intermediacy of PhN̈:, which has been reported[12] to have a triplet ground state, CIDNP experiments were carried out. Pyrolysis of **4** in decalin led to formation of aniline (10%); however, rapid scanning of the aromatic ^1H NMR (60 MHz) region of decalin solutions of **4** (0.5 M) at 130 and 140 °C failed to reveal enhanced absorption or emission signals. While selection of these reaction conditions for **4** ($\tau_{1/2}$ ~ 10 and 3 min, respectively) was based upon a suggested[13] rate-range for exploratory CIDNP studies, our negative results do not rule out a radical (triplet) precursor for aniline. The trimethylsilyl ^1H region was similarly monitored during pyrolysis of **4** in decalin, and neither CIDNP effects nor transient signals associated with trimethylsilyl group-bearing intermediates were evident. We also noted that the *N*- and *O*-trimethylsilyl group singlet absorptions for **4** showed no exchange broadening due to possible degenerate dyotropic rearrangement[14] (eq 6) during the course of its decomposition



(6)

in decalin at 140 °C. Similar dyotropic rearrangements have been found[15] for analogues of **4**; however, it is evident that further investigation of dyotropism in **4** will require an experimental probe other than ^1H NMR signal coalescence, such as deuterium labeling.[14b]

Utilization of *cis*- and *trans*-stilbene (**18** and **19**) as nitrene traps during thermolysis of **4** was patterned after studies by Abramovitch et al.,[11] which indicated that pentafluorophenylnitrene adds stereospecifically to these and other alkenes, presumably via a singlet species. Solutions of **4** in **18** as solvent (molar ratio **4**:**18** 1:25) were heated at 110 °C for 3 h,



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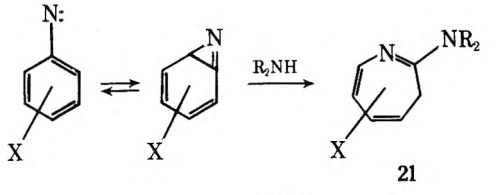
leading to ~90% reaction of **4**. Chromatography of the reaction mixture, which was complicated by the presence of a relatively large amount of soluble polymer, led to isolation of impure fractions containing trace amounts (<1%) of the expected 1,2,3-triphenylaziridine ring system (**20**); however, crystalline samples of **20** could not be obtained.[16] Azobenzene (**6**) was the major product. The yields of **20** from analogous experiments using **19** as the nitrene trap were too low to permit its detection, even with appropriate reaction scale-up and use of a 100-fold molar excess of **19**. Comparison of our reaction conditions (110 °C 3 h) with those reported by Huisgen and coworkers[17] for thermal ring opening of **20** (100 °C 60 h) indicates that the observed inefficiency of 1,2,3-triphenylaziridine production from **4** is real, rather than a consequence of thermally induced decomposition of **20** following its formation. It is interesting to note that while a dependence of aziridine yield on stilbene geometry was previously found[11] for pentafluorophenylnitrene, the relative efficiency order was opposit that presently reported, i.e., 0.6 and 32% yields of the aziridine from **18** and **19**, respectively. These differences are not understood at this time.

Production of 2-amino-3*H*-azepine derivatives (**21**) in reaction systems which generate arylnitrenes in the presence of amines is generally ascribed to intramolecular nitrene rearrangement to give 7-azabicyclo[4.1.0]heptatrienes followed by nucleophilic attack of amine (eq 7).[19] Extension of this trapping technique to thermolysis (100 °C) of **4** in a 125-fold molar excess of diethylamine solvent afforded $Me_3SiOSiMe_3$



(7)

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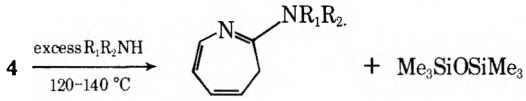


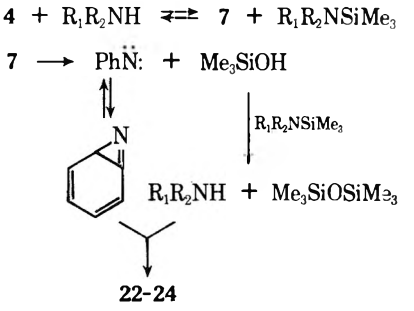
(8)

22, $R_1 = R_2 = Et$
23, $R_1 = R_2 = Bu$
24, $R_1 = H$; $= R_2 = c\text{-}C_6H_{11}$

and a 95% yield (VPC) of the well-characterized[20] 2-diethylamino-2*H*-azepine (**22**) product, without detactable amounts (<1%, VPC) of aniline (eq 8). A subsequent experiment revealed that the yield of azepine **22** was not appreciably altered upon lowering the relative proportion of diethylamine to only a tenfold molar excess. High yields (85–90%, VPC) of azepine products **23** and **24**, respectively, obtain for dibutylamine (Bu_2NH) and cyclohexylamine, even upon dilution of the reaction mixture with an inert solvent and further decrease of the molar excess of amine over **4** to a factor of 4–5. The virtual absence of aniline and the nonobservance of ^1H NMR CIDNP effects for **23** derived from rapid thermolyses of **4** ($\tau_{1/2}$ ~ 2 and 5 min) in Bu_2NH at 130 and 140 °C are consistent with (but do not demand) relatively facile intramolecular rearrangement of singlet PhN̈:. This possibility has been previously discussed[19a] with respect to diethylamine interception of rearranged ArN̈: obtained from phosphonite deoxygenation of nitroarenes.[21] Use of rigorously purified aniline, *p*-toluidine, or *N*-methylaniline as potential trapping agents failed to produce detectable amounts (<5%, NMR) of azepine.[22] Since Huisgen et al.[23] have previously reported isolation of a 2-anilinoazepine from pyrolysis of phenyl azide in aniline solvent, these contrasting results warrant further study.

In connection with the mechanistic details of eq 8, it was of importance to investigate the role, if any, played by the "trans-silylation" reaction shown in the first step of Scheme I. Production of **7** could conceivably be followed by its relatively rapid thermal (or amine-catalyzed) fragmentation to PhN̈: and trimethylsilanol, with ultimate formation of the observed azepine derivatives and $Me_3SiOSiMe_3$. Evidence contrary to the operation of this sequence of transformations derives from a number of experimental tests. Firstly, no ^1H NMR signals characteristic of **7** or Bu_2NSiMe_3 were detectable during slow thermolysis of **4** in Bu_2NH at 55 °C. Secondly, an equilibrium constant favoring the left-hand side of the "trans-silylation" step in Scheme I was not evidenced by

Scheme I



22-24

^1H NMR upon reaction of **7** with Bu_2NSiMe_3 in Bu_2NH solvent, which afforded **6**, azoxybenzene [PhN(O)=NPh], and $Me_3SiOSiMe_3$ at 130 °C. Thirdly, heating **7** in Bu_2NH at 130 °C led to formation of these latter three products without detectable amounts of **23** being produced. Fourthly, the disappearance rate of **4** upon heating in *o*-dichlorobenzene was found to be independent of the amount of added Bu_2NH.

Next studied was the yield of aniline produced during thermolysis of **4** as a function of the H-donating ability of the solvent. Solutions of **4** (0.1 M) in cyclohexane, cyclohexene, and toluene were each heated at 110 °C for a period of time (16 h) needed to achieve complete reaction. Quantitative VPC analyses indicated respective aniline yields of 19, 53, and 30%, with ±2% being the average deviation for triplicate determinations.[25] The cyclohexane system also gave a small amount (5%) of *N*-cyclohexylaniline, which has been previously shown[12] to arise from triplet PhN̈: during analogous thermal decomposition of phenyl azide. Normalization of these aniline yields to a basis of percent aniline per millimole of abstractable hydrogen from solvent gave relative values of 1.0:8.0:6.3, which qualitatively parallels the stability of radicals derived from these three solvents, respectively.[26] The high yield of dehydrogenated cyclohexene coupling product **16** (22%), relative to the amount of bibenzyl (1%) formed in toluene, may be reconciled by the possibility of 2-cyclohexenyl radical addition to cyclohexene. In any event, our data are consistent with a radical precursor to aniline. It is usually supposed[19a] that triplet arylnitrenes lead primarily to arylamine products; consequently, we explored the response of aniline yield from **4** to the presence of a heavy atom, which in some instances can promote intersystem crossing of singlet to triplet nitrenes.[28] For this study, the yield of aniline was determined (VPC, ±2%, average of duplicate runs) for completely reacted 0.1 M solutions of **4** in toluene containing increased molar proportions of *p*-bromotoluene. A plot of these results (Figure 1) reveals that a dramatic increase in aniline yield from 30 to 78% obtains, and that there is a roughly linear relationship between

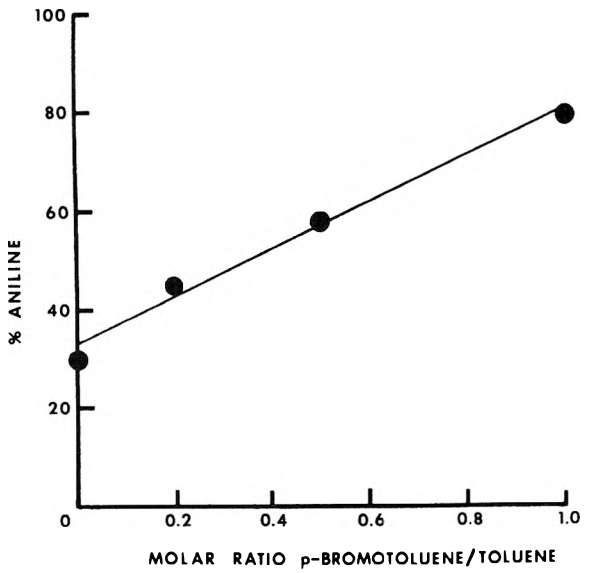


Figure 1. Plot of aniline yield (VPC, ±2%, average of duplicate runs) derived from complete thermolysis of **4** (0.1 M, 110 °C, 16 h) in toluene with increased amounts of *p*-bromotoluene.

this increase and the *p*-bromotoluene content of the reaction medium.

Solvent Trapping Studies for Thermolysis of 9. Comparative studies of **9** were hampered by the light sensitivity of this *O*-methyl analogue of **4**. For example, carefully prepared solutions of freshly purified (VPC) **9** in dry toluene changed from colorless to pale orange within hours at room temperature when not protected from light. The colored decomposition product was identified (TLC) as azobenzene (**6**). While handling and storage of **9** in the absence of light could virtually eliminate production of **6**, attempts to seal the Pyrex ampules used for pyrolysis resulted in variable amounts of sample degradation, with as much as a 50% decrease in the original concentration of **9**. Despite these difficulties, which attentuated our efforts, some reliable information regarding **9** was obtained. The thermal stability of **9** initially apparent from its survival during VPC isolation (100 °C residence time ~5 min) was confirmed in the course of kinetic studies (vide infra): 30% conversion of **9** took place after 34 h of heating at 90 °C in toluene to yield aniline (~15%) and **6** (~15%). While further heating results in the appearance and subsequently rapid formation of two unidentified products, it is worthwhile to note that an extrapolated aniline yield from **9** in toluene (~50% = ~15% × 100/30) is comparable to the amount of aniline (30%) derived from **4**. Low conversion studies with **9** also revealed substantial production (~50%, corrected) of methoxytrimethylsilane ($MeOSiMe_3$), as was anticipated by analogy to **4**. It thus appeared that while the initial mode of reaction for **9** parallels that of **4**, incursion of catalyzed side reactions becomes significant. A similarity in fragmentation characteristics between **9** and **4** in the gas phase was suggested by observing[29] that each of these compounds exhibits, upon electron impact (70 eV), a base peak at *m/e* 91 due to $C_6H_5N^{\cdot+}$.

Use of a ~100-fold molar excess of diethylamine as the pyrolysis solvent for **9** gave a minor product (~0.5%) having the same VPC retention time as **22**; however, positive identification of this material by TLC isolation could not be achieved. The yield of **6** was 15%. When a similar reaction was directly monitored by ^1H NMR, no azepine signals were detectable. The propensity of **8** toward formation of **6** (vide supra) suggested that this behavior of **9** in the presence of diethylamine, which markedly contrasts that of **4**, could be due to the intervention of a "trans-silylation" process (cf. Scheme I). Initial support for this possibility was obtained by ^1H NMR studies in $CDCl_3$, since treatment of **9** with 1 equiv of Bu_2NH led to relatively rapid formation of signals characteristic of **8** and Bu_2NSiMe_3. The production of Bu_2NSiMe_3 was confirmed by its VPC isolation and characterization by ir.

Table I. Kinetic Parameters for Thermolysis of *O*-Silylated *N*-Phenylhydroxylamine Derivatives in Toluene

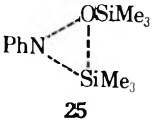
Compd	$[Compd]_0$, M	Temp, °C	$k \times 10^5$, sec^{-1} [a]	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
4 [b]	0.10	90	2.3	27.7	−3.8
	0.10	100	6.4		
	0.05	100	6.2		
	0.10	110	17.4		
9 [c]	0.20	70	0.032	27.6	−8.0
	0.10	70	0.036		
	0.05	70	0.031		
	0.20	80	0.11		
	0.20	90	0.32		
10	0.10	120	<0.03 [d]		

[a] First-order rate constant for disappearance of compound; obtained by standard VPC methods, except as indicated. [b] Approximately 80% reaction monitored. [c] Approximately 5–30% reaction monitored. [d] Limiting value based on <8% reaction after 80 h.

Kinetic Studies. As indicated in Table I, the disappearance rate constant (k) for **4** in toluene at 100 °C, which was obtained from a linear first-order decay plot, was independent of the initial concentration. Measurement of k for **4** at 90 and 110 °C thus afforded a linear least-squares fit of log (k/T) vs. T^{-1} giving $\Delta H^{\ddagger}$ = 27.7 kcal/mol and $\Delta S^{\ddagger}$ = −3.8 eu. Analogous behavior deduced for **9** (at low conversions), relative to **4**, was supported by finding first-order disappearance kinetics (5–30% reaction) for **9** with $\Delta H^{\ddagger}$ = 27.6 kcal/mol and $\Delta S^{\ddagger}$ = −8.0 eu. Determination of accurate rate data for **10** was foiled by nonreproducibility of data points and the small amounts of available **10**. However, a reliable value of $k < 3 \times 10^{-7}$ s^{-1} at 20 °C was obtained by finding in one case <8% reaction of **10** after 80 h of heating. Comparison of this limiting value with an extrapolated disappearance rate constant for **9** at 120 °C (k = 650 10^{-7} s^{-1}) indicated that **10** is at least 200 times less reactive than **9**.

The data presented in Table II demonstrate that the effect of solvent variation on k for **4** is small, with the rate being accelerated by a maximal factor of ~6.5 upon changing from hexafluorobenzene (ϵ 2.03) to benzonitrile (ϵ 25.20). By way of comparison, the relative disappearance rate ratio of ~4 exhibited by **4** in benzonitrile vs. decalin (ϵ 2.15) is somewhat greater than the relative rate ratio of ~1 reported for loss of nitrogen from either phenyl azide[30] or 2-azidobiphenyl[31] upon pyrolysis in nitrobenzene (ϵ 34.8) vs. decalin. The rates of methoxycarbene formation via thermal α-deoxysilylation have been found[1a] to be essentially identical in methanol vs. tetramethylethylene, which have widely different polarities.

Mechanism. A "concerted" elimination process for eq 1 has been previously suggested for α-deoxysilylation about C[1b] and Si.[2a] Evidence consistent with **4** undergoing similar one-step fragmentation via transition state **25** to $Me_3SiOSiMe_3$ and



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PhN: includes a number of observations: (a) the first-order fragmentation rate characterized by a negative $\Delta S^{\ddagger}$ [32] and small dependence on solvent polarity (ϵ), (b) the expected[5]

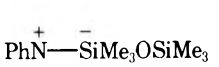
Table II. Effect of Solvent on the Thermolysis Rate of N,O-Bis(trimethylsilyl)-N-phenylhydroxylamine (4).

Solvent	$k \times 10^4$, s^{-1} [a]	Solvent	$k \times 10^4$, s^{-1} [a]
Hexafluoro-benzene	1.17	Cyclohexyl-amine	5.71
Decalin	1.90	o-Dichloro-benzene	5.45
Toluene	3.83[b]	Benzonitrile	7.50
Dibutylamine	4.47		

[a] First-order rate constant obtained by ^{1}H NMR techniques at 118 ± 3 °C over ~75% reaction, except as noted. [b] Calculated from activation parameters listed for 4 in Table I.

array of products obtained in the presence of cyclohexene, (c) isolation of **20** with *cis*-stilbene as the nitrene trap, (d) high azepine yields with alkylamine trapping agents, (e) the rational dependence of aniline yield on the nature of the four thermolysis solvents investigated, (f) isolation of *N*-cyclohexylaniline with cyclohexane as solvent, and (g) the absence of trimethylsilyl group-bearing intermediates via ^{1}H NMR monitoring experiments. Nucleophilic attack at silicon by oxygen implicit in **25** also provides a basis to understand the remarkable thermal stability of **7** (no reaction after 19 h at 100 °C), and **25** can be extended to its *O*-methyl analogues to account for the observed (Table I) disappearance rate inequities between **4**, **9**, and **10**: $k_4/k_9 = 7$ (90 °C) due to the electropositive[35a] nature of silicon vs. carbon, and $k_9/_{10} > 200$ (120 °C) due to increased steric hindrance of Et_3Si vs. Me_3Si.[35b]

A multistep fragmentation mode for **4** involving homolysis of the N–O bond to a tight radical pair followed by formation of intermediate **26** is an alternative possibility which is based



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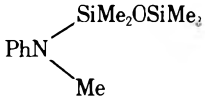

27

on very recent mechanistic suggestions by West and Nowakowski[36] to account for thermal rearrangement of tris(organosilyl)hydroxylamines (eq 2). If such a sequence is operative with **4**, **26** would be expected[36,37] to yield **27**; however, we have been unable to obtain evidence for aminodisiloxane **27** in direct ^{1}H NMR monitoring experiments. Consequently, this homolytic pathway either bypasses the intermediacy of **26** and leads directly to PhN: and $Me_3SiOSiMe_3$, or fragmentation of **26** to the nitrene and hexamethyldisiloxane is fast, relative to methyl migration giving **27**.[38] It should also be noted that rate-limiting N–Si bond homolysis in **4** to an anilino radical precursor to PhN: cannot be excluded. Further experiments with more electron-deficient derivatives of **4** and electron-rich stereoisomeric olefin traps are under investigation.

Experimental Section

Elemental analyses were performed by Chemalytics, Inc. ^{1}H NMR spectra were recorded on a Varian A-60 instrument at ambient probe temperature, using ~10% v/v solutions in deuteriochloroform and tetramethylsilane as an internal reference, except as noted. Ir and uv measurements were respectively obtained with Perkin-Elmer Model 337 and Cary Model 15 spectrophotometers. Aerograph 90-P and Varian Aerograph 920 thermal conductivity instruments were used with 0.25-in. columns, and a Varian Aerograph 940 flame-ionization gas chromatograph utilized 0.125-in. columns. Unless specified otherwise, Chromosorb G (60/80 mesh) was used throughout: column A, 3 ft × 0.25 in., 5% SE-30; column B, 6 ft × 0.25 in., 15% SE-30; column C, 18 × 0.25 in., 5% SE-30; column D, 6 ft × 0.25 in., 15% polyphenyl ether 5-ring; column E, 6 ft × 0.125 in., 15% OV-101 on High Performance Chromosorb G, 100/120 mesh; column F, 6 ft × 0.25 in., 15% Apiezon L on Chromosorb W, 60/80 mesh; column G, 3 ft × 0.25 in., 1% SE-30; column H, 5 ft × 0.125 in., 5% SE-30; column I, 18 × 0.25 in., 15% SE-30; column J, 3 ft × 0.125 in., 1% SE-30; column K, 18 × 0.25 in., 1% SE-30. VPC yields refer to comparison of peak areas obtained either with standardized solutions (constant injection volume) or with internal reference compounds.

All reactions were run under an atmosphere of high-purity nitrogen. Ether refers to commercial anhydrous ether; all solvents and amines were purified by standard procedures.[39] Chlorotriethylsilane, chlorotripropylsilane, and chlorodimethylphenylsilane (PCR, Inc.) were distilled prior to use, while chlorotrimethylsilane (Aldrich Chemical Co.) and *N,O*-bis(trimethylsilyl)acetamide (BSA, Pierce Chemical Co.) were used as received. Phenylhydroxylamine[40] (**5**) was recrystallized from cold ether–pentane and stored at 0 °C. *Caution:* **5** is a severe skin irritant.

Thermolysis reactions were carried out in degassed and sealed Pyrex ampules, which were heated in a constant-temperature (±0.2 °C) oil bath, unless specified otherwise.

***O*-Trimethylsilyl-*N*-phenylhydroxylamine (7).** A magnetically stirred solution of **5** (1.5 g, 13.8 mmol) in ether (40 ml) was maintained at −50 °C while 1 equiv of butyllithium in hexane (1.67 M) was slowly added (30 min). Additional stirring (1–3 h) was followed by dropwise introduction (15 min) of chlorotrimethylsilane (3.5 ml, 27.6 mmol) in ether (10 ml) solution. The temperature of the reaction mixture was then allowed to gradually (1.5 h) rise to room temperature and after an additional period of time (2 h), LiCl was removed by gravity filtration under a blanket of N_2. Volatiles from the filtrate were removed in vacuo (1 mm) at room temperature and the residual oil was Kugelrohr distilled to yield (53%) a golden-colored liquid (bp 70–90 °C, 1 mm), which was identified as **7**: NMR δ 7.33–6.40 (m, 6, aromatic and NH) and 0.23 (s, 9, $SiMe_3$); ir (neat) 3050, 2970, 2900, 2390, 1601, 1500, 1260, and 720 cm^{-1}. Analytically pure **7** was obtained by preparative VPC on column G (95 °C, 120 ml/min).

Anal. Calcd for $C_9H_{15}NOSi$: C, 59.62; H, 8.34; N, 7.72. Found: C, 59.44; H, 8.47; N, 8.14.

***N,O*-Bis(trimethylsilyl)-*N*-phenylhydroxylamine (4).** A solution of **5** (1.5 g, 13.8 mmol) in ether (40 ml) was treated with 2 equiv of butyllithium in hexane (1.67 M), and then with excess chlorotrimethylsilane (7 ml, 55.7 mmol), in the same manner as described for the preparation of **7**. The reaction mixture was stirred at −50 °C (30 min) and the temperature was then allowed to rise to −20 °C: recooling to −50 °C followed by warming to −20 °C was repeated three more times. After final stirring at room temperature for 12 h, workup as with **7** and then Kugelrohr distillation gave **4** (40%) as a golden-colored oil (bp 40–85 °C, 1 mm); use of the theoretical amount of chlorotrimethylsilane (3.5 ml, 28 mmol) consistently gave **4** in ~20% yield, with increased amounts of by-product **6**. Ultimate purification of **4** was achieved by preparative VPC of the distillate on column G (95 °C, 120 ml/min): NMR δ 6.47–8.33 (m, 5, aromatic), 0.17 (s, 9, $OSiMe_3$), 0.10 (s, 9, $NSiMe_3$); ir (neat) 3080, 3050, 2975, 2915, 1600, 1490, 1260, 1175, 1083, 1032, 965, 850, 760, 700, and 625 cm^{-1}; λ_{max} (C_6H_{12}) nm (log ε 3.88).

Anal. Calcd for $C_{12}H_{23}NOSi_2$: C, 56.86; H, 9.15; N, 5.53. Found: C, 57.16; H, 9.32; N, 5.64.

Reaction of **5** according to general silylation procedures with either Et_3N/Me_3SiCl[6] or BSA in pyridine[7] led to isolation of mainly **6** upon workup and distillation of the crude product mixture.

***O*-Methyl-*N*-phenylhydroxylamine (8).** The following modified procedure of Walter and Schaumann resulted in a yield of **8** which was twice that reported by these authors. A solution of recrystallized *N,N'*-diphenyl-*N*-methoxyurea (31 g, 0.128 mol) in diethylamine (65 ml) was gently refluxed for 13 h with protection from light. After removal of diethylamine on a rotary evaporator at room temperature, the residue was subjected to rapid Kugelrohr distillation and yielded (35%) **8** as a pale yellow oil (bp 40–75 °C, 0.5 mm). ^{1}H NMR analyis was consistent with that reported for **8** (δ_{OCH_3} 3.75), and no methoxyl absorption (δ 3.35) from methanol contamination was evident. Decomposition of **8** into **6** and methanol may be effectively retarded by storage at low temperatures as a dilute solution in, e.g., ether. Kugelrohr distillation of a partially decomposed sample of **8** leads to separation of pure **8** from **6**, which remains as pot residue.

An ether solution of pure **8** (~0.1 M) was treated at −40 °C with 1 equiv of butyllithium in hexane (2 M) and was then allowed to warm to room temperature. The orange-colored solution was quenched with water and VPC analysis of the organic layer confirmed the presence of primarily **6**.

***O*-Methyl-*N*-phenyl-*N*-trimethylsilylhydroxylamine (9).** A solution of **8** (1.0 g, 8.1 mmol) in ether was sequentially reacted with 1 equiv of butyllithium in hexane (2 M) and 1 equiv of chlorotrimethylsilane as in the case of **4**. Precipitation of lithium chloride was first noted at ~0 °C. The usual workup followed by Kugelrohr dis-

tillation afforded **9** (43%) as a pale yellow oil (bp 60 °C, 0.5 mm): NMR δ 6.50–7.50 (m, 5, aromatic), 3.51 (s, 3, OMe), 0.23 (s, 9, $SiMe_3$); ir (neat) 3090, 3070, 3025, 2950, 2890, 2810, 1600, 1480, 1250, 1028, 938, 890, 840, 750, 695, and 620 cm^{-1}. VPC purification utilized column C (100 °C, 120 ml/min); significant amounts of other components having t_{air} values similar to **9** were not observed.

Toluene solutions (~0.1 M) of freshly collected pure **9** [λ_{max} (C_6H_{12}) 247 nm (log ε 3.93)] when allowed to stand at room temperature in the presence of light turned to a pale orange color after ~3 h; TLC analysis indicated the presence of **6**. Brief exposure of a frozen solution of pure **9** (0.1 M) in toluene to light emitted from molten Pyrex during ampule sealing was found (VPC) to result in variable amounts of decomposition, with as much as 50% decrease in the initial concentration of **9**.

Anal. Calcd for $C_{10}H_{17}NOSi$: C, 61.49; H, 8.77. Found: C, 61.67; H, 9.05.

***O*-Methyl-*N*-phenyl-*N*-triethylsilylhydroxylamine (10).** Seqential reaction of **8** (0.60 g, 4.8 mmol) with 1 equiv of buthyllithium and chlorotriethylsilane, as in the preparation of **9**, was followed by stirring at 0 °C for 7 days, during which time gradual precipitation of lithium chloride was noted. The usual workup and then Kugelrohr distillation led to collection of two fractions (bp 35–55 and 55–95 °C, 0.5 mm), which were both found by VPC analysis on column A (110 °C, 120 ml/min) to contain **6** (t_{air} = 6 min) and one additional major component (t_{air} = 4 min). Collection of the latter material led to its identification as **10** (7%): NMR δ 6.66–7.50 (m, 5, aromatic), 3.57 (s, 3, OMe), and 1.25–0.65 (m, 15, $SiEt_3$); ir (neat) 3050, 2960, 2910, 2880, 2805, 1600, 1490, 1245, 1026, 1004, 825, 740, and 695 cm^{-1}.

Anal. Calcd for $C_{13}H_{23}NOSi$: C, 65.77; H, 9.77; N, 5.90. Found: C, 65.77; H, 9.59; N, 6.12.

Attempted Synthesis of *O*-Methyl-*N*-phenyl-*N*-tripropylsilylhydroxylamine (11) and *N*-Dimethylphenylsilyl-*O*-methyl-*N*-phenylhydroxylamine (12). Reaction of **8** with butyllithium and then with either chlorotripropylsilane or chlorodimethylphenylsilane was carried out in the same manner as that described for **10**. In both cases, VPC analysis with column A (110 °C, 120 ml/min) of the Kugelrohr distillate (bp ~50–120 °C 0.5 mm) indicated the presence of mainly unreacted chlorosilane and **6**; additional minor components (<~5%) were not collected for identification.

***N*-Trimethylsilyldibutylamine.** A solution of butyllithium (31 mmol) in hexane (2 M) was added over a period of 0.5 h to a magnetically stirred solution of dibutylamine (6 ml, 35 mmol) in ether (50 ml) at −10 °C. After further stirring for 0.5 h, chlorotrimethylsilane (4 ml, 32 mmol) was added (0.5 h) to the cold solution and the mixture was then allowed to stir at ambient temperature (12 h). Lithium chloride was removed by gravity filtration under a blanket of N_2 and the filtrate was concentrated in vacuo (15 mm). VPC analysis using column A (90 °C, 120 ml/min) revealed the presence of essentially one product (t_{air} = 6.3 min), which was collected by preparative VPC and identified as *N*-trimethylsilyldibutylamine: NMR δ −0.04 (s, 9, $SiMe_3$), 0.65–1.70 (m, 14), 2.40–2.90 (m, 4, NCH_2); ir (neat) 1164 cm^{-1} (Si–N). The hydrolytic instability of this product was evident from the appearance and rapid increase in intensity of a Si–O bond at 830 cm^{-1} during ir analysis.

7-Phenyl-7-azabicyclo[4.1.0]heptane (14) and *N*-Phenylcyclohexylideneimine (17). Following the procedure of Clark,[41] phenyl azide (130 mg, 1.1 mmol) in cyclohexene (5 ml) was refluxed for 36 h (80% theoretical N_2 evolution). The reaction mixture was diluted with chloroform, filtered, concentrated on a rotary evaporator, and then Kugelrohr distilled to give a pale yellow oil (81 mg, bp 80–90 °C, 1 mm) that was found by VPC on column A (105 °C, 60 ml/min) to be a 60:40 mixture of two components having t_{air} values of 15 and 20 min, respectively. These two materials were isolated by preparative VPC and the faster eluting was identified as **14** by its ^1H NMR and ir spectra.[41] The slower eluting component was characterized as **17**: NMR δ 7.60–6.45 (m, 5, aromatic), 2.60–1.95 (m, 4, allylic), and 1.95–1.30 (m, 6); ir (neat) 1710 cm^{-1} (C=N). Positive identification of **17** was achieved by comparison with material that was prepared by condensation of aniline with cyclohexanone.

Thermolyses of 4. Cyclohexene Solvent. A solution of **4** (700 mg, 2.8 mmol) in cyclohexene (28 ml, 0.28 mol) was heated at 100 °C for 16 h. Volatiles were removed in vacuo (1 mm) at room temperature and a chloroform solution of the residue was subjected to preparative VPC using column A (100 °C, 120 ml/min). Aniline (t_{air} = 45 s) and **14** (t_{air} = 7.5 min) were isolated in 20 and 2% yields, respectively, and were identified by comparison (ir, ^1H NMR) with authentic material. Bicyclohexyldiene **16**[42] (100 mg, 22%; t_{air} = 3.4 min) was characterized by spectral and elemental analysis: δ 5.53 (broad s, 4, vinylic), 2.55–1.08 (m, 14); ir (neat) 3020, 2930, 2860, 2840, 1450, 1440, 1138, 899, 874, 867, 724, 647, and 600 cm^{-1}.

Anal. Calcd for $C_{12}H_{18}$: C, 88.82; H, 11.18. Found: C, 89.08, 88.80; H, 11.42, 11.10.

Product **15** (4%, t_{air} = 10 min), which consumed 1 equiv of H_2 upon microhydrogenation over Pd/C in absolute ethanol, was identified spectroscopically: NMR δ 7.16–6.26 (m, 5, aromatic), 5.69 (s with additional splitting, 2, vinylic), 3.88 (m, 1, methine), 3.25 (broad s, 1, NH), 2.34–1.08 (m, 6, methylenes); ir (neat) 3410, 3050, 3025, 2930, 2855, 1601, 1500, 1430, 1320, 1260, 1248, 747, 725, and 691 cm^{-1}. Trace amounts of **17** (<1%) and **6** (<1%) were identified by coinjection with authentic samples on column E (120 °C, 15 ml/min), and two additional products (<1%) with t_{air} values similar to **17** remain uncharacterized. TLC (silica gel, ether) of the crude pyrolysis mixture confirmed the presence of **6** and indicated the formation of a relatively large amount of noneluting brown polymer. VPC analysis (column F, 60 °C, 60 ml/min) of the pyrolysis mixture before product isolation indicated that the yield of $Me_3SiOSiMe_3$ was ~100%, within experimental error (±10%), based on peak area comparisons with a solution of authentic $Me_3SiOSiMe_3$ of known concentration. Heating a solution of **14** in cyclohexene (0.1 M) for 14 h at 120 °C was shown, by VPC techniques, not to lead to production of detectable (<5%) amounts of either **15** or **17**.

Stilbene Solvents. A solution of **4** (200 mg, 0.8 mmol) in *cis*-stilbene (**18**, 4 ml, 20 mmol) was heated at 110 °C for 3 h. Unreacted **18** was removed by Kugelrohr distillation (80 °C, 0.5 mm) and the pot residue was subjected to preparative TLC (alumina, 30–60 °C petroleum ether). Residual **18** and a relatively large amount of **6** were detected as overlapping fast-eluting bands (R_f 0.8–0.9); two slow-eluting bands (R_f 0.7 and 0.4) were collected. ^1H NMR (220 MHz) analyses of each of these samples revealed a singlet absorption (δ 3.64) characteristic[17] of ring system **20**; however, the low integrated signal intensity ratio of this singlet to the aromatic protons indicated substantial contamination. The yield of **20** was roughly estimated to be <1%. Microcrystallization techniques failed to give a solid sample of **20**. Repetition of the above experiment using a mixture of **4** (3.5 g, 14 mmol) in *trans*-stilbene (**19**, mp 122–124 °C, 24.9 g, 0.14 mol) heated at 125 °C for 25 min did not give a detectable amount of **20**. Dissolution of a 1:10 molar mixture of **4**:**19** in a minimal amount of o-dichlorobenzene, followed by heating at 110 °C for 3 h, gave similar negative results for the formation of **20**.

Diethylamine Solvent. A solution of **4** (200 mg, 0.8 mmol) in diethylamine (10 ml, 0.1 mol) was heated at 100 °C for 62 h, concentrated on a rotary evaporator, and then analyzed by VPC using column G (100 °C 120 ml/min). A portion of the major product, which had the same retention time (3 min) as **4**, was collected and identified as **22** based on the reported[20] ^1H NMR spectrum of this azepine. Quantitative VPC measurements performed on the remaining crude material revealed a 95% yield of **22**; no aniline was detectable (<1%) by VPC, and only trace amounts (~1%) of **6** and azoxybenzene were seen. Similar results were obtained in a repeat experiment wherein **4** (200 mg, 0.8 mmol) was heated in diethylamine (0.8 ml, 8 mmol) at 100 °C for 16 h.

Anal. Calcd for $C_{10}H_{16}N_2$: C, 73.12; H, 9.82; N, 17.06. Found: C, 73.22; H, 9.86; N, 17.56.

Dibutylamine Solvent. A sample of **4** in a 100-fold molar excess of dibutylamine was reacted as above and volatiles (bp <~40°) were then removed by Kugelrohr distillation at reduced pressure (1 mm). The pot residue was subjected to preparative TLC (silica gel, 95:5 30–60 °C petroleum ether–ether) and the broad fluorescent band (R_f 0.3), which readily separated from a small amount of faster eluting by-product **6**, was further purified by preparative VPC on column A (130 °C, 120 ml/min) and identified as **23** from the close similarity of its ^1H NMR vinyl and allyl absorptions to that of **22**. Quantitative VPC measurements indicated that the yield of **23** was 85%.

Anal. Calcd for $C_{14}H_{24}N_2$: C, 76.31; H, 11.00; N, 12.70. Found: C, 76.13; H, 11.23; N, 12.47.

A similarly high azepine yield was obtained when **4** (100 mg, 0.4 mmol) and dibutylamine (0.30 ml, 1.76 mmol) were heated (55 °C) in an NMR tube for a period of 5 days; trimethylsilyl group signals characteristic of **7** (δ ~0.23) and Bu_2NSiMe_3 (δ ~0) were not observed during the course of this reaction. Reaction of a mixture of **7** (0.3 M) and Bu_2NSiMe_3 in dibutylamine at 130 °C was directly monitored by NMR over a period of 13 h. Characteristic signals for Me_3SiO-$SiMe_3$, **6**, and azoxybenzene increased in intensity with time; however, neither **23** nor trimethylsilyl group signals indicative of **4** were detectable during the course of reaction. An NMR tube containing a solution of **7** (~1 M) in dibutylamine was monitored at 130 °C for 2 h. Azepine **23** was not detectable; however, signals for $Me_3SiOSiMe_3$, **6**, and azoxybenzene were evident. Production of the latter three products was confirmed by a combination of ir and VPC analysis.

Cyclohexylamine Solvent. A solution of **4** (70 mg, 0.28 mmol) in

cyclohexylamine (0.33 ml, 28 mmol), which had been heated at 118 °C for 2 h, was analyzed by VPC using column C (140 °C, 120 ml/min) and the major product (t_{air} = 6.5 min) was collected as a pale yellow colored solid (mp 118–119 °C, 30–60 °C petroleum ether). Structure **24** was assigned to this material (88% yield, VPC) on the basis of ^{1}H NMR spectral similarities with **22**.

Anal. Calcd for $C_{12}H_{18}N_2$: C, 75.74; H, 9.53. Found: C, 75.88; H, 9.76.

Attempted CIDNP Detection. A degassed ^{1}H NMR sample of **4** in decalin (0.5 M) was inserted into the preequilibrated and precalibrated (ethylene glycol) spectrometer probe at 130 ± 2 °C. After 30 s, repetitive scans (500-Hz sweep width, 100-s sweep time) of the aromatic proton region were obtained over ~30-s time intervals for 20 min; no evidence for CIDNP was apparent. In a duplicate experiment, the decreasing intensity of the $NSiMe_3$ and $OSiMe_3$ singlets at 0 and 6 Hz (relative) was accompanied by a comparable increase in the singlet absorption for $Me_3SiOSiMe_3$ at 1.5 Hz; the fragmentation half-life was ~10 min and neither CIDNP nor additional $SiMe_3$ signals were in evidence. Omission of the degassing in sample preparation had no effect on these results. Repetition of the experiments at 140 °C ($\tau_{1/2}$ ~ 3 min) gave similar results and a 10% yield (VPC) of aniline. No significant decrease in the chemical shift difference between the $SiMe_3$ signals in **4**, or broadening of these signals ($W_{1/2}$), was evident at 140 °C, relative to spectra obtained at 35 °C. Pyrolyses of **4** in dibutylamine (0.5 and 1.3 M) at 130 °C were monitored (1000-Hz sweep width, 50-s sweep time) in the azepine ring proton region of **23** over ~30-s time intervals. CIDNP effects were not seen in these experiments, as well as in one at 140 °C (0.5 M), while near-exclusive production of **23** was evident from subsequent TLC analyses.

Determination of Aniline Yield from Thermolysis of 4 in Various Solvents. Three aliquots from each stock solution (0.1 M) prepared from **4** (20 mg, 0.08 mmol) and the various solvents 0.8 ml) were sealed in vacuo in small Pyrex ampules and heated simultaneously at 110 °C for 16 h. Complete reaction of **4** was evidenced by VPC on column G (90 °C, 120 ml/min) and the yield of aniline in each case was determined by VPC peak area comparisons (cut and weigh technique) with a standardized 0.1 M solution of aniline, using column F (105 °C, 120 ml/min): cyclohexane, 19%; cyclohexene, 53%; toluene, 28%; *p*-bromotoluene, 78%. The average deviation among all samples was ±2%. The homogeneity of the aniline peak derived from *p*-bromotoluene was established by comparison with pure aniline using combined VPC–mass spectrometry techniques. A 1 ± 0.05% yield of bibenzyl from the toluene system was determined by quantitative VPC analyses on columns E (150 °C) and J (105 °C). Repetition of the above experiment using duplicate 0.1 M solutions of **4** in pure toluene, and in 80:20 and 50:50 mol % toluene–*p*-bromotoluene mixtures gave 32, 45, and 58 ± 2% aniline, respectively.

Thermolysis of 9 in the Presence of Diethylamine. A frozen solution of compound **9** (195 mg, 1 mmol) in diethylamine (10 ml, 0.096 mol) was sealed quickly in a Pyrex ampule and was then heated at 110 °C for 36 h. After removal of solvent in vacuo, a small amount (15%) of unreacted **9** was detected by VPC using column C (100 °C, 120 ml/min) and was then collected for positive identification by ir. Azobenzene (15%) and a minor component (~0.5%) having the same retention time as the expected product **22** were also present; however, the latter material could not be isolated by TLC in sufficient quantities to confirm its tentative identification as **22**.

A frozen solution of pure **9** (0.4 M) in diethylamine was sealed in vacuo in an NMR tube; the ^{1}H spectrum indicated that no detectable photochemical decomposition of **9** had taken place (vide supra). Upon heating at 110 °C, gradual reaction to yield signals characteristic of **6** was evident; however, no absorptions for azepine **22** could be seen. In a control experiment, a $CDCl_3$ solution of **9** (0.5 M) and Bu_2NH (0.5 M) was sealed in an NMR tube and heated at 55 °C; only **8** and Bu_2NSiMe_3 were evident from their respective OCH_3 and $SiMe_3$ signals after 14 h. Preparative VPC of this NMR sample gave pure **8** (NMR) and Bu_2NSiMe_3 (ir 1165 cm^{-1}, Si–N).

Kinetic Studies. Compound 8. A 0.20 M solution of freshly distilled **8** in toluene containing *o*-dibromobenzene (0.02 M) as an internal VPC reference was heated at 40 ± 0.5 °C in a small Pyrex tube (5 × 50 mm; ~0.5 ml volume) equipped with a well-greased ground glass stopcock. A tight-fitting rubber septum cap allowed for periodic removal of VPC samples and immediate analysis on column I (90 °C, 100 ml/min). A standard[43] second-order kinetic plot of $([8]_0 - x)^{-1} - [8]_0^{-1}$ vs. time was linear over the monitored reaction period (48 h) and gave $2k = 1.46 \times 10^{-6}$ M^{-1} s^{-1}, where $[8]_0$ is the initial concentration of **8** and x is the concentration of **6** at time t. Duplicate constant volume VPC injections demonstrated that the *o*-dibromobenzene did not undergo a detectable amount (<5%) of reaction. Repetition with 0.10 and 0.05 M solutions of **8** gave values of $2k$ = 7.00 and 2.60×10^{-7} M^{-1} s^{-1}, respectively, indicating a reaction order n = 2.04 ± 0.06.

Compound 4. Predried Pyrex ampules containing aliquots (~0.2 ml) of a 0.10 M solution of purified **4** in toluene containing *o*-dibromobenzene (0.02 M) as an internal VPC reference were sealed in vacuo and heated in a constant temperature oil bath at temperatures of 90, 100, and 110 ± 0.2 °C. Tubes were removed periodically, stored at 0 °C, and analyzed under constant VPC conditions using column A (100 °C, 120 ml/min). Duplicate constant volume injections confirmed the inertness of *o*-dibromobenzene under the reaction conditions. Linear least-squares fits (±5–10% slope error) of first-order plots of ln $([4]_0/[4]_t)$ vs. t gave the values of k listed in Table I. A comparative run at 100 °C and an initial concentration of **4** equal to 0.05 M demonstrated the unimolecular character of kinetics for **4**. A least-squares fit (±5% slope error) of log (k/T) vs. T^{-1} afforded the activation parameters given in Table I.

Measurement of k for **4** as a function of solvent was accomplished by ^{1}H NMR at a probe temperature of 118 ± 3 °C and using 0.50 M samples. Relative $SiMe_3$ signal intensities (cut and weigh method) for starting material and the $Me_3SiOSiMe_3$ fragmentation product were utilized to calculate $[4]_t$. Linear first-order plots (±5% slope error) were manually obtained over the monitored reaction period (~50%) and gave the values of k listed in Table II. The effect of added dibutylamine (0.17, 0.33, and 0.66 M) on the thermolysis rate of **4** (0.33 M) in *o*-dichlorobenzene was similarly studied and was found to be negligible.

Compound 9. VPC purified **9** was immediately diluted with toluene containing 0.02 M *o*-dichlorobenzene, as an internal VPC reference, to give 0.20, 0.10, and 0.05 M solutions, which were then heated (in the absence of light) at 70 ± 0.1 °C using the same type of reaction vessels as described above for **8**. VPC samples from each solution were removed at 20-h intervals for 6 days (5–30% reaction) and were analyzed on column H (90 °C, 15 ml/min). Linear least-squares fits (±5% slope error) of ln $([9]_0/[9]_t)$ vs. t gave first-order rate constants (Table I) having an average value of $k = 3.3 \pm 0.2 \times 10^{-7}$ s^{-1}. In the 0.20 M run, after 28% reaction, the only two products detected by VPC were a 1:1 ratio of aniline and **6**. After ~30–40% reaction, the rate of disappearance of **9** noticeably accelerated, without further production of aniline or **6**. Instead, the decrease in **9** was accompanied by appearance of unidentified peaks having retention times comparable to and twice that of **6**.[44] A 50% (corrected) yield of methoxytrimethylsilane ($MeOSiMe_3$) at low conversion was determined by VPC using column F (75 °C, 60 ml/min) and a standardized solution of independently synthesized[45] $MeOSiMe_3$. Two unidentified VPC peaks with slightly shorter retention times than $MeOSiMe_3$ may be associated with the low yield of $MeOSiMe_3$ via possible thermal and/or catalyzed disproportionation reactions; however, $MeOSiMe_3$ in toluene was shown to be thermally stable under the reaction conditions. Addition of a catalytic amount of aniline had no observable effect on this stability.

Compound 10. A sample of **10** that had been purified twice by preparative VPC was dissolved in anhydrous toluene to give a 0.09 M stock solution; recrystallized biphenyl (0.02 M) was used as an internal VPC reference. In order to obtain reasonably reproducible VPC ratios of **10**:biphenyl (±4%), a newly prepared and conditioned column (K, 100 °C, 70 ml/min) was necessary. Sealed Pyrex ampules containing aliquots of the stock solutions were heated (120 ± 0.1 °C) in an oil bath for various time intervals and then analyzed under constant VPC conditions. A first-order disappearance plot for **10** was initially linear over a 24-h time period (~25% reaction) and then exhibited large deviations indicative of catalytic acceleration. In a duplicate run, no reaction was detectable (<8%; maximum error associated with VPC analysis) after 80 h of heating at 120 °C.

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Registry No.—**4**, 53783-47-4; **5**, 100-65-2; **6**, 103-33-3; **7**, 58751-79-4; **8**, 32654-23-2; **9**, 55563-84-3; **10**, 59859-53-9; **14**, 18713-90-1; **15**, 52034-22-7; **16**, 1541-20-4; **17**, 1132-38-3; **22**, 6798-41-0; **23**, 59859-54-0;

24, 59859-55-1; chlorotrimethylsilane, 75-77-4; *N,N'*-diphenyl-*N*-methoxyurea, 59859-56-2; chlorotriethylsilane, 994-30-9; *N*-trimethylsilyldibutylamine, 3553-86-4; dibutylamine, 111-92-2; aniline, 62-53-3; *cis*-stilbene, 645-49-8; *trans*-stilbene, 103-30-0; diethylamine, 109-89-7; cyclohexylamine, 108-91-8.

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Reaction of 2,3-Diphenyl-5,6-dihydropyrazine and Malononitrile to Give 2,6-Diamino-3,5-dicyano-4,10-diphenyl-1,7-diazatricyclo[5.2.1.0^{4,10}]deca-2,5-diene. A Novel Synthesis of a Substituted Diazadihydrotriquinacene

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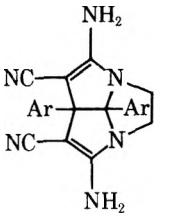
The reactions of 2,3-diphenyl-5,6-dihydropyrazine (1) and 2,3-di(*p*-fluorophenyl)-5,6-dihydropyrazine with malononitrile to give 2,6-diamino-3,5-dicyano-4,10-diphenyl-1,7-diazatricyclo[5.2.1.0^{4,10}]deca-2,5-diene (2) and 2,6-diamino-3,5-dicyano-4,10-di(*p*-fluorophenyl)-1,7-diazatricyclo[5.2.1.0^{4,10}]deca-2,5-diene (6) in 70 and 61% yield, respectively, are reported. The structure proofs for 2 and 6 are based on spectral properties and hydrolytic and decarboxylative conversions to 3 and 7 as well as x-ray structure analysis of 3. The mechanism of the rearrangement involved in the formation of 2 is discussed and 2 is noted to be a readily available precursor to a substituted diazatriquinacene system.

Investigation of an alleged heterophilic addition to nitrogen has prompted reports that the reaction of hydrogen cyanide with 2,3-diphenyl-5,6-dihydropyrazine (1) is, in fact, normal.[1,2] Accordingly, the heterophilic course suggested for the reaction of 1 with malononitrile[3] seems unlikely and has been reinvestigated. We now wish to report that the product of this reaction is 2,6-diamino-3,5-dicyano-4,10-diphenyl-1,7-diazatricyclo[5.2.1.0^{4,10}]deca-2,5-diene (2) and to note that this rearrangement may provide a novel and efficient entry to the diazatriquinacene systems.



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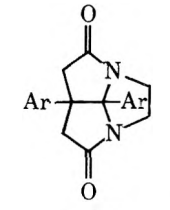
6, Ar = *p*-FC_6H_4



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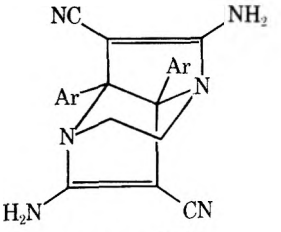
7, Ar = *p*-FC_6H_4



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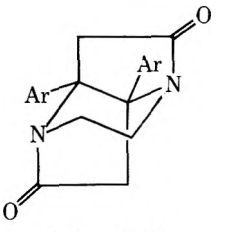


5, Ar = C_6H_5

Results and Discussion

Reaction of 1 with 2 equiv of malononitrile in 20 ml of 95% ethanol at reflux for 1 h provides a 70% yield of material with an empirical formula of $C_{22}N_6H_{18}$ as shown by analysis and mass spectrometry. The presence of an enaminonitrile function in this compound is revealed by its infrared and ultraviolet spectra. The former has absorptions attributable to amino and nitrile functions at 3226–3300 cm^{-1} and 2174 cm^{-1}, while the latter has a chromophore for the enaminonitrile at λ_{max} 256 nm (ϵ 22 000).[4-6] The NMR spectrum of this material indicates the presence of two phenyl groups, four exchangeable protons, and two methylene groups. The latter are in an apparent AA'BB' system.

Treatment of $C_{22}N_6H_{18}$ with 50% sulfuric acid provides in 27% yield a compound $C_{20}H_{18}N_2O_2$, as expected for hydrolytic and decarboxylative conversion of an enaminonitrile to a carbonyl derivative.[4] The infrared spectrum of this hydrolytic product shows strong carbonyl absorption at 1718 and 1698 cm^{-1} (sh) consistent with a ring fused γ-lactam, while the NMR spectrum shows four new protons in two equivalent methylene groups (J_{AB} = 17 Hz) as well as ten aromatic and four AA'BB' protons.

Of the possible structures we consider to be mechanistically reasonable for the above reactions, 2 and 3 provide the best agreement to the above data for the enaminonitrile and the lactam, respectively. Of the many alternatives[6] only 4 and its hydrolytic product 5 require further consideration.

The principal difference in the structures under consideration lies in the symmetry of the carbons bearing the phenyl groups. In the case of 2 and 3, these carbons are located on the molecular mirror plane and are nonequivalent. For structures 4 and 5, however, these carbons are located symmetrically about a C_2 axis and are formally equivalent. The ^{13}C NMR of the enaminonitrile product shows two peaks at δ 66.2 and 99.1 ppm which are attributable to nonequivalent carbons bearing phenyls in accord with structure 2. The hydrolytic product, 3, shows peaks at δ 49.7 and 97.1 ppm, which can be similarly assigned.

In order to make certain of the nonequivalence of the aromatic rings, 2,3-di(*p*-fluorophenyl)-5,6-dihydropyrazine was prepared and allowed to react with 2 equiv of malononitrile to provide a compound $C_{22}H_{16}F_2N_6$. This material had infrared, ultraviolet, and NMR spectral properties which, except for the bands associated with the phenyl groups, were very similar to those of 2. The ^{19}F spectrum of this material showed two peaks at δ 112.9 and 115.0 ppm consistent with structure 6. Hydrolysis of 6 with sulfuric acid gave 7, a compound which also showed nonequivalence of the phenyl groups in its ^{13}C and ^{19}F spectra. To confirm these assignments the structure of 3 was determined by x-ray structure analysis.

The crystals of 3 are orthorhombic, the space group is *Pbca*, and there are eight molecules of $C_{20}H_{18}N_2O_2$ in the unit cell. The structure was solved by direct methods[7] and has been refined to values of R and R_w of 0.066 and 0.060 on 1355 nonzero reflections. The final model was obtained by least-squares refinement of the positional and anisotropic thermal parameters for the nonhydrogen atoms and the positional and isotropic thermal parameters for the hydrogen atoms. A stereoscopic view of the molecular structure of 3 is shown in Figure 1.

The final atomic coordinates and full list of bond lengths and angles will appear in the microfilm edition. The individual values do not require extensive comment although the C(4)–C(10) bond [1.587 (7) Å] appears to be lengthened owing to the overcrowding of the three nonhydrogen substituents on each atom. The departure of the molecule in the solid from formal C_s symmetry is quite striking. While part of the reason for this effect may be due to intermolecular forces, the steric

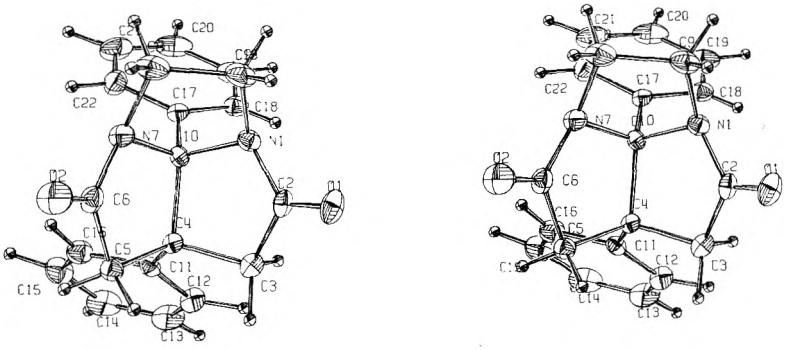
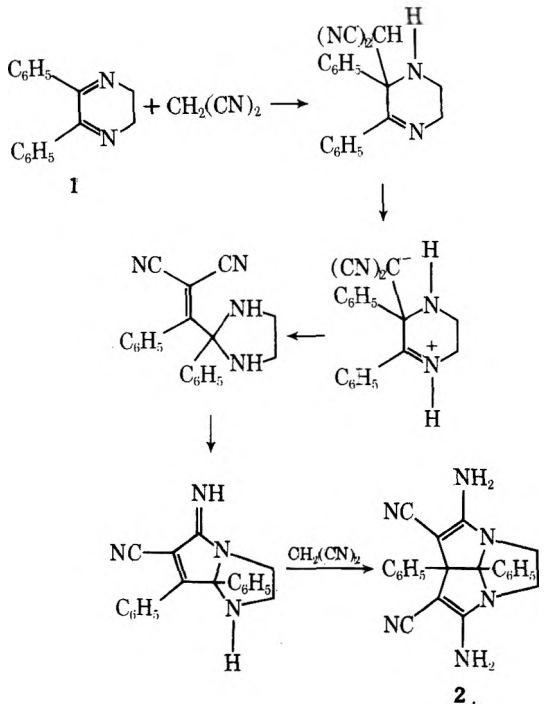


Figure 1. Stereo pair showing a single molecule of **3**.

overcrowding due to the fully substituted central C(4)–C(10) bond causes very significant departures from the fully eclipsed conformation of substituents around that bond; the C(11)–C(4)–C(10)–C(17), C(3)–C(4)–C(10)–N(1), and C(5)–C(4)–C(10)–N(7) torsion angles are −12.4, −11.3, and −5.4°, respectively. This twist of substituents about C(4)–C(10) will induce dissymmetry in the molecule and cause minor variations in the conformations of the two nitrogen-containing rings and in the spatial dispositions of the attached phenyl groups (Figure 1).

There are no unusually short intermolecular contacts; a feature of the packing is the number of contacts in the range 3.34–3.60 Å involving a carbonyl oxygen atom. A list of the shorter contacts will appear in the microfilm edition.

The structural assignments to **2** and **6** as products of the reaction of diaryldihydropyrazines and malononitrile raise the question as to how this rearrangement proceeds. A formal proposal is shown in which addition of the malononitrile to the imine bond provides a zwitterion in which ring contraction of the tetrahydropyrazine ring is promoted by formation of a double bond which is conjugated with a phenyl ring and two nitrile groups. The rearrangement finds formal analogy in the benzilic acid rearrangement[8a] and amino groups migrations to electron-deficient centers.[8b] Analogous additions involving malononitrile are well known.[8c] The simplicity of this synthesis and its potential for the synthesis of a diazatriquinacene are noted.[9]



Experimental Section[10]

***p,p'*-Difluorobenzil** was prepared from 7.89 g of *p*-fluorobenzaldehyde (Aldrich Chemical Co.) and a solution of 0.75 g of potassium cyanide in 24 ml of 2:1 ethanol–water in a manner analogous to the preparation of benzil.[11] Extractive workup with benzene gave 7.39 g of an orange-yellow oil, which was heated on a steam bath with 40 ml of glacial acetic acid and 20 ml of concentrated nitric acid for 2 h. Dilution with 150 ml of water gave *p,p'*-difluorobenzil as a light yellow precipitate. Recrystallization from methanol provided 2.65 g (34%) of yellow needles: mp 120–121 °C; ir (Nujol) 1670 s, 1600 s, 1502 m, 1235 s, 1210 m, 1155 s, 888 s, 843 s, 798 m, 760 m, 746 cm^{-1} m; ^1H NMR ($CDCl_3$) δ 7.00–7.46 (m, 4, meta H's), 7.84–8.10 (m, 4, ortho H's); ^{19}F NMR ($CDCl_3$) δ 101.7 (t of t, J = 8.5 and 5.5 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 246 (3.9, M^+), 123 (100.0), 95 (35.2), 75 (12.9).

Anal. Calcd for $C_{14}H_8F_2O_2$: C, 68.29; H, 3.28; F, 15.43. Found: C, 68.07; H, 3.01; F, 15.28.

A second crop of 702 mg (9%) of material with mp 118–120 °C was also collected.

2,3-Di(*p*-fluorophenyl)-5,6-dihydropyrazine was synthesized by heating 3.20 g (0.013 mol) of *p,p'*-difluorobenzil and 0.811 g (0.013 mol) of 98% ethylenediamine in 25 ml of ethanol at reflux for 1 h.[12] The 1.81 g (52%) of yellow crystals obtained in cooling the reaction mixture had mp 103–106 °C; ir (Nujol) 1590 s, 1560 m, 1500 s, 1310 m, 1265 m, 1230 s, 1210 s, 1155 s, 983 s, 860 m, 842 s, 833 s, 817 m, 809 cm^{-1} m; ^1H NMR ($CDCl_3$) δ 7.43–6.73 (m, 8, *p*-FC_6H_4), 3.62 (s, 4, $-CH_2CH_2-$); ^{19}F NMR ($CDCl_3$) δ 110.9 (t of t, J = 8.5 and 5.5 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 270 (25.4, M^+), 122 (13.7), 121 (100.0).

Anal. Calcd for $C_{16}H_{12}N_2F_2$: C, 71.10; H, 4.48; N, 10.37; F, 14.06. Found: C, 70.95; H, 4.53; N, 10.34; F, 14.02.

Synthesis of 2,6-Diamino-3,5-dicyano-4,10-diphenyl-1,7-diazatricyclo[5.2.1.0^{4,10}]deca-2,5-diene (2). A mixture of 4.68 g (0.02 mol) of 2,3-diphenyl-5,6-dihydropyrazine and 2.65 g (0.04 mol) of malononitrile in 20 ml of 95% ethanol was heated at reflux for 1 h.[3] After cooling, the crystals which precipitated were collected by filtration and washed with ethanol. Trituration with hot ethanol afforded 5.87 g of faintly brown fluffy material which was a 1:1 solvate[3] of **2** with ethanol according to the NMR spectrum (Me_2SO-d_6). This material was dried in vacuo at 78 °C overnight to give 5.07 g (70%) of **2**: mp 341 °C dec (lit.[3] 340 °C dec); ir (Nujol) 3436, 3300, 3226, 3165, 2174, 1637, and 1585 cm^{-1}; uv max (95% ethanol) 256 nm (ε 22 000) and 214 (10 500); ^1H NMR (Me_2SO-d_6) δ 6.98 (br s, 10, C_6H_5), 6.83 (s, 4, NH_2, exchanges with deuterium oxide), 3.33 (AA'BB', 4, $-CH_2CH_2-$); ^{13}C NMR (Me_2SO-d_6) δ 164.0 ($C_{2,6}$), 138.9, 138.2, 128.5, 126.8, 126.1 (ArC), 119.7 (CN), 99.1 (C_{10}), 66.2 (C_4), 63.4 ($C_{3,5}$), 48.2 ($C_{8,9}$); mass spectrum (70 eV) *m/e* (rel intensity) 366 (11.5, M^+), 229 (90.2), 126 (68.3), 91 (35.4), 84 (33.4), 82 (31.8), 62 (42.3), 60 (49.5), 43 (72.5), 30 (100.0).

Anal. Calcd for $C_{22}N_6H_{18}$: C, 72.11; H, 4.95; N, 22.93. Found: C, 71.86; H, 4.93; N, 22.90.

Synthesis of 2,6-Diamino-3,5-dicyano-4,10-di(*p*-fluorophenyl)-1,7-diazatricyclo[5.2.1.0^{4,10}]deca-2,5-diene (6). A mixture of 2.14 g (7.9 mmol) of 2,3-di(*p*-fluorophenyl)-5,6-dihydropyrazine and 1.06 g (16 mmol) of malononitrile in 7 ml of ethanol was heated at reflux for 2 h. The precipitate which appeared was collected by filtration, washed with ethanol, and dried at 78 °C (0.1 mm) overnight to give 2.464 g (61%) of **6**: mp 341 °C dec; ir (Nujol) 3322 m, 2179 vs, 1660 m, 1631 vs, 1590 s, 1500 vs, sh, 1230 s, 1154 s, 868 m, 830 cm^{-1} m; uv max (95% ethanol) 212 nm (ε 15 300), 257 (19 800); ^1H NMR (Me_2SO-d_6) δ 2.32–3.85 (AA'BB', 4, $-CH_2CH_2-$), 6.67–7.22 (m, 12,

C_6H_4F and NH_2, addition of deuterium oxide reduces integration to 8 H); ^{19}F NMR (Me_2SO-d_6) δ 114.9 (t of t, 1 F, J = 8.5 and 5.5 Hz),[13] 116.1 (t of t, 1 F, J = 8.5 and 5.5 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 403 (27.6), 402 (100.0, M^+), 359 (11.1), 332 (19.1), 331 (20.6), 319 (13.3), 242 (50.4), 241 (45.6), 122 (14.2), 43 (12.7).

Anal. Calcd for $C_{22}H_{16}F_2N_6$: C, 65.66; H, 4.01; N, 20.89; F, 9.44. Found: C, 65.42; H, 4.00; N, 21.16; F, 9.66.

Hydrolysis of 2,6-Diamino-3,5-dicyano-4,10-diphenyl-1,7-diazatricyclo[5.2.1.0^{4,10}]deca-2,5-diene. Formation of 3. A suspension of 2.01 g (5.5 mmol) of **2** in 90 ml of 50% sulfuric acid was heated at gentle reflux for 3 h. The yellow reaction mixture was allowed to cool to room temperature, poured onto 100 g of crushed ice, and neutralized with ammonium hydroxide. Extraction with chloroform provided 1.33 g of slightly yellow-brown solid. Chromatography on 50 g of alumina with benzene and chloroform–benzene provided 0.767 g of crude dilactam **3**, mp 225–230 °C. Rechromatography on 40 g of silica gel with chloroform as eluent gave 663 mg of material, mp 234–239 °C. Recrystallization from aqueous ethanol gave 464 mg (27%) of **3** as white plates: mp 239–240 °C; ir (KBr) 1722 vs, 1703 sh, 1380 s, 1312 m, 1260 m, 1017 m, 957 m, 772 m, 760 m, 703 s, and 498 cm^{-1} m; ^1H NMR ($CDCl_3$) δ 7.02 (m, 10, C_6H_5), 3.62 (AA'BB', 4, $-CH_2CH_2-$), 3.25 (AB, 4, $-CH_2-$, J = 17 Hz, $\Delta\nu_{AB}$ = 53 Hz); ^{13}C NMR ($CDCl_3$) δ 177.9 ($C_{2,6}$), 140.3, 135.4, 128.1, 127.8, 127.7, 127.0 (ArC), 97.1 (C_{10}), 49.7 (C_4), 48.1 ($C_{8,9}$), 44.3 ($C_{3,5}$); mass spectrum (70 eV) *m/e* (rel intensity) 319 (22.5), 318 (100.0, M^+), 317 (22.6), 262 (19.9), 260 (18.8), 248 (17.9), 247 (41.9), 246 (27.5), 241 (10.1), 220 (10.1), 117 (28.2), 115 (20.3), 104 (12.6), 103 (10.9), 91 (21.1), 77 (16.0), 70 (23.6), 43 (14.6), 42 (18.8), 32 (14.8), 31 (19.0), 28 (21.6).

Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.55; H, 5.88; N, 8.97.

Hydrolysis of 1,7-Diazatricyclo[5.2.1.0^{4,10}]-4,10-di(*p*-fluorophenyl)-2,6-diamino-3,5-dicyanodeca-2-5-diene. Formation of 7. A suspension of 1.039 g (2.6 mmol) of **6** in 45 ml of 50% sulfuric acid was heated at reflux for 4 h. Workup by extraction with chloroform and chromatography on alumina provided 322 mg of a faintly brown solid, mp 201–207 °C. Recrystallization of this material from aqueous ethanol afforded 242 mg (26%) of dilactam **7** as colorless needles: mp 206–208 °c; ir (Nujol) 1726 vs, 1710 vs, 1600 m, 1500 s, 1360 s, 1300 m, 1224 s, 1165 m, 1156 m, 1015 m, 928 m, 850 m, 833 m, and 702 cm^{-1} m; ^1H NMR ($CDCl_3$) δ 7.28–6.62 (m, 8, *p*-FC_6H_4), 3.23 (AB, 4, $-CH_2-$, J = 17.5 Hz), 3.62 (AA'BB', 4, $-CH_2CH_2-$); ^{13}C NMR ($CDCl_3$) 177.6 ($C_{2,6}$), 162.7, 161.6, 136.0, 131.4, 128.7, 128.6, 115.5, 115.3 (ArC), 96.7 (C_{10}) 49.3 (C_4), 48.0 ($C_{8,9}$), 44.4 ($C_{3,5}$); ^{19}F NMR ($CDCl_3$) δ 112.9 (t of t, 1 F, J = 5.2 and 8.3 Hz), 115.0 (t of t, 1 F, J = 5.2 and 8.3 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 355 (24.7), 354 (100.0, M^+), 353 (22.9), 298 (31.5), 297 (11.8), 296 (19.6), 284 (26.6), 283 (50.4), 282 (29.0), 256 (31.7), 254 (12.3), 205 (14.1), 136 (12.7), 135 (50.0), 134 (11.0), 133 (25.1), 122 (18.7), 121 (13.0), 115 (14.2), 95 (15.4), 70 (39.0), 42 (26.9).

Anal. Calcd for $C_{20}H_{16}N_2O_2F_2$: C, 67.79; H, 4.55; N, 7.91; F, 10.72. Found: C, 67.51; H, 4.47; N, 7.86; F, 10.32.

X-Ray Analysis of 4,10-Diphenyl-2,6-dioxo-1,7-diazatricyclo[5.2.1.0^{4,10}]decane (3). Crystals of **3** as white, transparent needles elongated in the c direction were obtained from absolute ethanol. An untwinned crystal with dimensions ca. 0.2 × 0.1 × 0.3 mm was used for data collection. Crystal data: $C_{20}H_{18}N_2O_2$, mol wt 318.4, orthorhombic, a = 24.229 (9), b = 15.449 (7), c = 8.796 (3), U = 3292.4 × 10^{-24} cm^3, Z = 8, D_c = 1.28 g/cm^3, μ (Cu Kα) = 6.82 cm^{-1}, F (000) = 1344, systematic absences $0kl$, when $k = 2n + 1$, $h0l$, when $l = 2n + 1$, and $hk0$, when $h = 2n + 1$ establish the space group as $Pbca$, λ (Cu Kα) = 1.54178 Å.

The intensity data were collected on a computer-controlled four-angle Syntex $P2_1$ diffractometer using a 2θ scan mode with variable scan speeds. Scan speeds ranging from 2°/min to 10°/min were determined for individual reflections by a fast scan of the peak maximum. The background to scan time ratio used was 0.25. A total of 2814 independent reflections was scanned in the 2θ sphere from 0° to 130° with graphite-monochromatized Cu Kα radiation (λ = 1.54178 Å). Out of these reflections, 1355 were considered to be significantly above zero at the 2σ level, as determined by counting statistics.

The structure was solved by direct methods.[7] Several cycles of full-matrix least-squares refinement of the positional and anisotropic thermal parameters for the nonhydrogen atom converged to an R factor of 0.103 and R_w of 0.106. The weights were taken as $1/[\sigma(F_o)^2 + (0.02F_o)^2]$, where $\sigma(F_o)$ is the standard deviation based on counting statistics. All the hydrogen atoms were located from a difference map and then included in the refinement with isotropic thermal parameters. The final R factor was 0.066 and R_w was 0.060. The value of $[\Sigma w \Delta^2/(m - n)]^{1/2}$ was 1.40. The scattering curves were taken from the analytical expressions used in "International Tables for X-Ray Crystallography".[14] The final values for the thermal parameters and the list of structure factors will appear in the microfilm edition.

Acknowledgment. This work was supported by the National Institutes of Health and the National Science Foundation. The x-ray work was carried out on a Syntex $P2_1$ diffractometer, EXTL computer system, and XD3 Structure Graphics system whose purchase was made possible by an NSF Major Equipment Chemistry Departmental Grant (MPS 75-05911) to the University of Illinois. We are grateful for the support. The structure determination was part of a class project and we acknowledge the contributions and participation of William Baker, Monique Hinterberger, Philip Urnezis, and John Zeigler.

Registry No.—**1**, 1489-06-1; **2**, 59873-34-6; **3**, 59873-35-7; **6**, 59873-36-8; **7**, 59873-37-9; *p,p'*-difluorobenzil, 579-39-5; *p*-fluorobenzaldehyde, 459-57-4; 2,3-di(*p*-fluorophenyl)-5,6-dihydropyrazine, 59873-38-0; ethylenediamine, 107-15-3; malononitrile, 109-77-3.

Supplementary Material Available. Full details of the x-ray determination (7 pages). Ordering information is given on any current masthead page.

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Unsymmetrically 3,6-Disubstituted *s*-Tetrazines. Synthesis of 3-Aryl-6-(perfluoroalkyl)-1,2,4,5-tetrazines and 1,2-Dihydro Derivatives

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A method for the synthesis of 1,2-dihydro-3-aryl-6-(perfluoroalkyl)-1,2,4,5-tetrazines, **8**, from which 3-aryl-6-(perfluoroalkyl)-1,2,4,5-tetrazines, **9**, are obtained by oxidation has been developed. Treatment of a variety of aroylhydrazides, **10**, with perfluorinated aliphatic aldehydes (or their hydrates or hemiacetals) gave 2-(1-hydroxyperfluoroalkyl)aroylhydrazides, **11**, from which perfluorinated aliphatic aldehyde aroylhydrazones, **1**, were produced by dehydration. Treatment of both **11** and **1** with thionyl chloride produced 1-aryl-1-chloro-4-(perfluoroalkyl)azines, **3**, which on treatment with chlorine in carbon tetrachloride or glacial acetic acid afforded 1-aryl-1,4-dichloro-4-(perfluoroalkyl)azines, **7**. Reaction of **7** with hydrazine hydrate, methylhydrazine, and 1,2-dimethylhydrazine gave the title compounds (**8**).

Most of the monocyclic *s*-tetrazines reported in the literature are symmetrically disubstituted compounds.[1,2] Unsymmetrically substituted *s*-tetrazines are considerably more difficult to synthesize, and there are no methods of synthesis that are common for all types. Symmetrical 3,6-diaryl-*s*-tetrazines are available from the reaction of hydrazine with 1,4-diaryl-1,4-dichloroazines, derived from diaroylhydrazines by treatment with phosphorus pentachloride,[3-6] or by chlorination of diarylazines.[7] Here the 1,2-dihydro-*s*-tetrazines are the primary products from which the *s*-tetrazines are obtained by oxidation. We have now examined approaches to the synthesis of 3-aryl-6-(perfluoroalkyl)-*s*-tetrazines, **9**, by way of perfluorinated aliphatic aldehyde aroylhydrazones, **1**, and aromatic aldehyde perfluoroalkanoylhydrazines, **2**.

Results and Discussion

Of the four potential approaches to 1-aryl-1,4-dichloro-4-(perfluoroalkyl)azines, **7**, from acylated aldehyde hydrazones, **1** and **2**, only the first one (path a) has been successful in our hands. The applicability of the other three (path b, c, and d) appears to be limited. For example, attempted chlorination of **1** (X = H; $R_F = CF_3$) in glacial acetic acid failed to give detectable amounts of **4** (X = H; $R_F = CF_3$) after several hours at 35 °C. When **2** (X = H; $R_F = C_3F_7$) was treated with refluxing thionyl chloride containing a small amount of dimethylformamide, the desired chloroazine, **5** (X = H; $R_F = C_3F_7$), was indeed formed in 10–15% yield, but was difficult to separate from by-products. Chlorination of **2** (X = H; $R_F = CF_3$) in glacial acetic acid at 45 °C gave α-chlorobenzaldazine (86%); at 65 °C, the only product isolated was benzal chloride (42%).

In view of the apparent insensitivity of aroylhydrazones, **1**, toward chlorine and the sensitivity toward both chlorine and thionyl chloride of hydrazones **2**, it was surprising that treatment of the **1** compounds with refluxing thionyl chloride gave chloroazines of general structure **3** in good yields and of acceptable purity (80–90%).

For the conversion of **3** into 1,4-dichloroazines, **7**, chlorination in glacial acetic acid or carbon tetrachloride proved satisfactory and gave the desired compounds in good yields (54–100%) and acceptable purity (60–90%) as highly viscous, reactive amber oils. In light of the reactivity of the key intermediates, **7**, no attempt was made to distill them; characterization and determination of purity was by NMR and thin layer chromatography. Depending on the nature of the substituent on the benzene ring, the time required for complete chlorination varied widely both in glacial acetic acid and carbon tetrachloride. Electronegative substituents on phenyl increased the period, e.g., 2–5 h were required for unsubstituted and alkyl-substituted **3**, whereas 12 days were needed for **3** (X = 3-CF_3) at ambient temperature. Progress of chlorinations could be followed by thin layer charomatography.

In one instance, the chlorination procedure led to an unexpected side reaction, 1-chloro-1-(3,5-dimethylphenyl)-

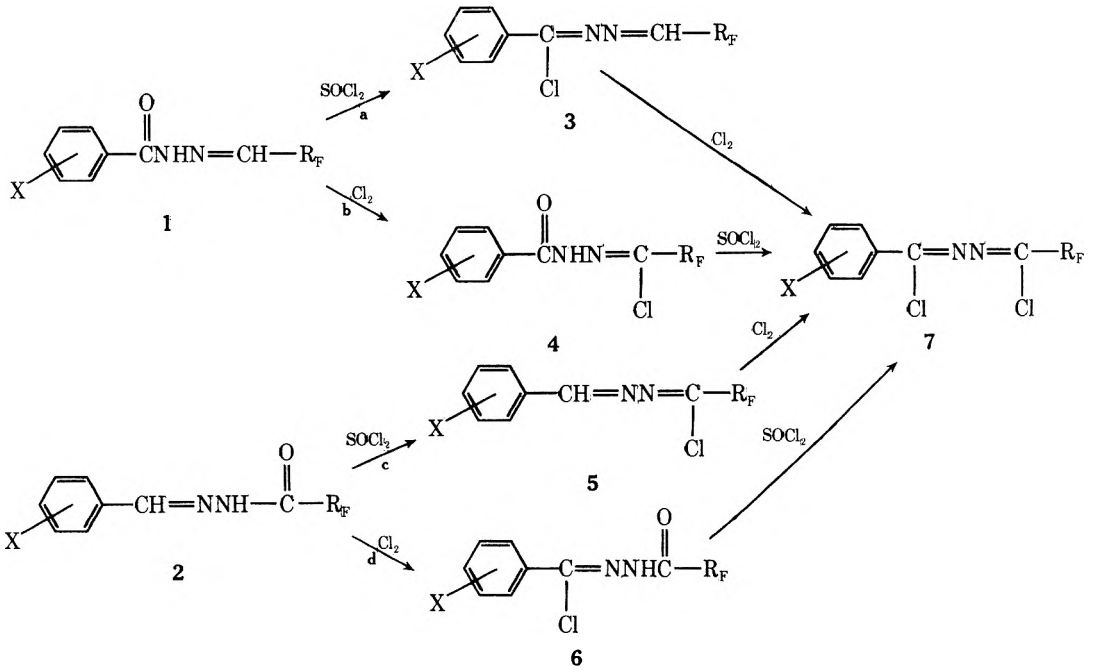


Table I. 1,2-Dihydro-3-aryl-6-(perfluoroalkyl)-1,2,4,5-tetrazines, 8,[a] and 3-Aryl-6-(perfluoroalkyl)-1,2,4,5-tetrazines, 9[a]

				8				9			
X	R^1	R^2	R_F	% yield	Mp, °C	Molecular formula	Registry no.	% yield	Mp, °C	Molecular formula	Registry no.
H	H	H	CF_3	95	159–161	$C_9H_7F_3N_4$	54820-09-6	81	154–156	$C_9H_5F_3N_4$	56349-37-2
H	H	CH_3	CF_3	33	133–136	$C_{10}H_9F_3N_4$	59872-85-4				
H	CH_3	CH_3	CF_3	32	75–78	$C_{11}H_{11}F_3N_4$	59872-86-5				
H	H	H	C_2F_5	79	161–163	$C_{10}H_7F_5N_4$	54820-10-9	51	117–120	$C_{10}H_5F_5N_4$	56349-40-7
H	H	H	C_3F_7	80	162–164	$C_{11}H_7F_7N_4$	54820-11-0	42	87–89	$C_{11}H_5F_7N_4$	56349-38-3
2-F	H	H	CF_3	33	155–157	$C_9H_6F_4N_4$	59872-87-6	21	68–71	$C_9H_4F_4N_4$	59872-91-2
4-Cl	H	H	CF_3	5	175–177	$C_9H_6ClF_3N_4$	54820-17-6	10	92–94	$C_9H_4ClF_3N_4$[b]	56349-44-1
4-Cl	H	H	C_2F_5	8	157–159	$C_{10}H_6ClF_5N_4$	59872-88-7	90	84–86	$C_{10}H_4ClF_5N_4$	59872-92-3
4-Cl	H	H	C_3F_7	47	140–143	$C_{11}H_8ClF_7N_4$	59872-89-8	92	62–64	$C_{11}H_4ClF_7N_4$	59872-93-4
3,4-Cl_2	H	H	CF_3					4	90–92	$C_9H_3Cl_2F_3N_4$	56349-46-3
3-CF_3	H	H	CF_3	10	132–134	$C_{10}H_6F_6N_4$	54820-13-2				
3-CH_3	H	H	CF_3	73	116–120	$C_{10}H_9F_3N_4$	54820-12-1	30	64–66	$C_{10}H_7F_3N_4$	56349-39-4
4-CH_3	H	H	CF_3	67	188–191	$C_{10}H_9F_3N_4$	54820-15-4	90	152–154	$C_{10}H_7F_3N_4$	56349-42-9
3,4-$(CH_3)_2$	H	H	CF_3	94	149–152	$C_{11}H_{11}F_3N_4$	54820-18-7	28	65–67	$C_{11}H_9F_3N_4$	56349-45-2
3,5-$(CH_3)_2$	H	H	CF_3					22	125–128	$C_{11}H_9F_3N_4$	56349-48-5
3,5-$(CH_3)_2$, 4-Cl	H	H	CF_3	20	197–200	$C_{11}H_{10}ClF_3N_4$[c]	54820-14-3	12	133–135	$C_{11}H_8ClF_3N_4$[d]	56349-41-8
4-$C(CH_3)_3$	H	H	CF_3	81	116–119	$C_{13}H_{15}F_3N_4$	54820-16-5	62	73–75	$C_{13}H_{13}F_3N_4$	56349-43-0
4-NO_2	H	H	CF_3					3	129–131	$C_9H_4F_3N_5O_2$	56349-47-4
3,4-CH=CHCH=CH	H	H	CF_3	56	203–205	$C_{13}H_9F_3N_4$	59872-90-1	27	189–192	$C_{13}H_7F_3N_4$	59872-94-5

[a] All compounds were analyzed for C, H, and N. Except where noted, the results obtained were within ±0.4% of the calculated values. [b] Nitrogen: calcd, 21.5; found, 18.9. [c] Carbon: calcd, 45.4; found 44.4. [d] Carbon: calcd, 45.8; found, 45.2.

4-(trifluoromethyl)azine, **3** [X = 3,5-$(CH_3)_2$; R_F = CF_3], being converted, at 55 °C, rather easily into 1-(4-chloro-3,5-dimethylphenyl)-1,4-dichloro-4-(trifluoromethyl)azine, **7** [X = 4-Cl-3,5-$(CH_3)_2$; R_F = CF_3]. However, chlorination at ambient temperature proceeded smoothly to give **7** [X = 3,5-$(CH_3)_2$; R_F = CF_3] in quantitative yield.

Both 1-chloro- and 1,4-dichloro-1,4-diarylazines have been used as starting materials in heterocyclic synthesis[8–13] and the mechanism of the nucleophilic substitution has been studied in detail.[14] We found that dichloroazines, **7**, also reacted, at 0 °C, in ethanol with hydrazine, methylhydrazine, and 1,2-dimethylhydrazine. Under these conditions, 1,2-dihydro-2-aryl-6-(perfluoroalkyl)-1,2,4,5-tetrazines, **8**, were formed and isolated as tan to light yellow crystalline solids. Yields were generally satisfactory depending on the purity of the precursor 1,4-dichloroazine, **7**. The 1,2-dihydro-s-tetrazines so prepared are listed in Table I.

Unambiguous proof of the 1,2-dihydro-*s*-tetrazine structure, **8**, for the reaction products of **7** with hydrazine lies in their conversion by oxidation into the orange to purple-red *s*-tetrazines, **9**. In the present work, oxidation was conveniently and rapidly accomplished by the dropwise addition at 0–25 °C of an aqueous solution of sodium nitrite or ferric chloride to a stirred solution containing **8** in water or ethanol, or alternatively, with hydrogen peroxide in acetic acid. The results of the oxidations are summarized in Table I.

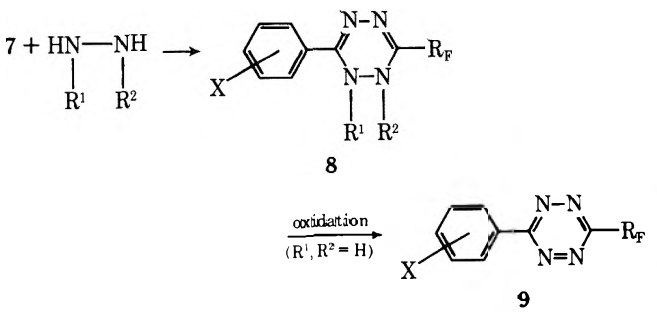


Table II. 2-(1-Hydroxy-2,2,2-trifluoroethyl)-benzoylhydrazides, 11[a]

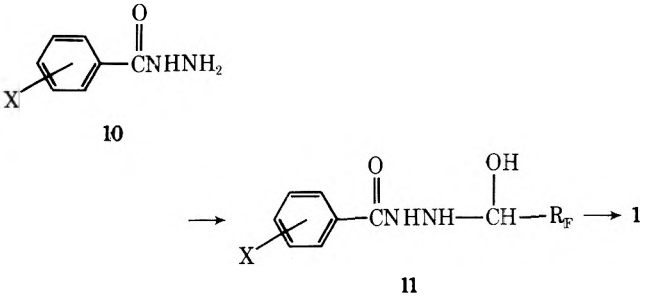
X	% yield	Mp, °C[b]	Molecular formula	Registry no.
H	89	169–171	$C_9H_9F_3N_2O_2$	54820-19-8
2-F	100	125–128	$C_9H_8F_4N_2O_2$	59872-95-6
4-Cl	94	162–164	$C_9H_8ClF_3N_2O_2$	59872-96-7
3-CH_3	85	132–134	$C_{10}H_{11}F_3N_2O_2$	59872-97-8
4-CH_3	76	200–203	$C_{10}H_{11}F_3N_2O_2$	59872-98-9
3,4-$(CH_3)_2$	65	184–187	$C_{11}H_{13}F_3N_2O_2$	59872-99-0
3,5-$(CH_3)_2$	89	185–188	$C_{11}H_{13}F_3N_2O_2$	59888-80-1
4-$C(CH_3)_3$	95	162–165	$C_{13}H_{17}F_3N_2O_2$	59873-00-6

[a] Satisfactory analytical data were obtained for all compounds listed in this table (±0.4% for C, H, and N). [b] With decomposition (dehydration).

Experimental Section

Materials. Trifluoroacetaldehyde hydrate, pentafluoropropionaldehyde methyl hemiacetal, heptafluorobutyraldehyde ethyl hemiacetal, and trifluoroacetyl chloride were obtained commercially.

Perfluorinated aliphatic aldehyde aroylhydrazones, **1**, were prepared by the following route. In this synthesis, a hydrazide, **10** (prepared by literature procedures), was allowed to react with a perfluorinated aldehyde, R_F-CHO (or its hydrate or hemiacetal), to give **11**



from which **1** was obtained by dehydration. The products, **11** and **1**, so obtained are listed in Tables II and III, respectively.

Table III. Perfluorinated Aliphatic Aldehyde Aroylhydrazones, 1[a]

X	R_F	% yield	Mp, °C	Molecular formula	Registry no.
H	CF_3	67	191–193	$C_9H_7F_3N_2O$	54820-20-1
H	C_2F_5	81	150–152	$C_{10}H_7F_5N_2O$	54820-23-4
H	C_3F_7	80	118–120	$C_{11}H_7F_7N_2O$	583-14-2
2-F	CF_3	100	170–172	$C_9H_6F_4N_2O$	59873-01-7
4-Cl	CF_3	80	203–205	$C_9H_6ClF_3N_2O$	59873-02-8
4-Cl	C_2F_5	88	171–173	$C_{10}H_6ClF_5N_2O$	59873-03-9
4-Cl	C_3F_7	83	138–140	$C_{11}H_6ClF_7N_2O$	59873-04-0
3-CH_3	CF_3	100	151–153	$C_{10}H_9F_3N_2O$	59873-05-1
3,5-$(CH_3)_2$	CF_3	61	185–188	$C_{11}H_{11}F_3N_2O$	59873-06-2
4-$C(CH_3)_3$	CF_3	45	208–210	$C_{13}H_{15}F_3N_2O$	59873-07-3
2-Cl	CF_3	82	190–192	$C_9H_6ClF_3N_2O$	59873-08-4
3,4-Cl_2	CF_3	97	168–170	$C_9H_5Cl_2F_3N_2O$	59872-47-8
4-NO_2	CF_3	86	240–242	$C_9H_6F_3N_3O_3$	59872-48-9
3-CF_3	CF_3	93	138–141	$C_{10}H_6F_6N_2O$	59872-49-0
3,5-$(CF_3)_2$	CF_3	56	204–207	$C_{11}H_5F_9N_2O$	59872-50-3
3,4-CH=CHCH=CH	CF_3	100	208–210	$C_{13}H_9F_3N_2O$	59872-51-4

[a] Satisfactory analytical data were obtained for all compounds listed in this table (±0.4% for C, H, and N).

Benzaldehyde Trifluoroacetylhydrazone, 2 (X = H; R_F = CF_3). This compound was prepared in 20% yield from benzalhydrazone and trifluoroacetyl chloride in tetrahydrofuran (−20 °C) containing 1 molar equiv of triethylamine, mp 132–135 °C.

Anal. Calcd for $C_9H_7F_3N_2O$: C, 50.8; H, 3.2; N, 13.0. Found: C, 50.5; H, 3.4; N, 13.1.

Benzaldehyde Heptafluorobutyrylhydrazone, 2 (X = H; R_F = C_3F_7). This compound was prepared in 96% yield from heptafluorobutyric acid hydrazide (mp 75–77 °C) and benzaldehyde in ethanol containing several drops of concentrated hydrochloric acid and had mp 95–98 °C.

Anal. Calcd for $C_{11}H_7F_7N_2O$: C, 41.8; H, 2.2; N, 8.9. Found: C, 41.9; H, 2.2; N, 8.7.

The general procedures used for the steps 11 → 1 → 3 → 7 → 8 → 9 are illustrated using two examples.

1,2-Dihydro-3-phenyl-6-(trifluoromethyl)-1,2,4,5-tetrazine, 8 (R^1, R^2, X = H; R_F = CF_3). A. 2-(1-Hydroxy-2,2,2-trifluoroethyl)benzhydrazide, 11 (X = H; R_F = CF_3). To a warm (55 °C) solution containing 110 g (0.81 mol) of benzhydrazide in 600 ml of water was added with stirring 99.6 g (0.86 mol) of trifluoroacetaldehyde hydrate, causing a white solid to precipitate almost instantaneously. The stirred reaction mixture then was heated to 80–90 °C for 1 h, cooled to room temperature, and filtered to give 128 g of colorless solid. Concentration of the filtrate to dryness gave 30.6 g of additional solid. The total product, 169.4 g (89%), was a colorless solid: ir (KBr) 3100 (NH), 1650 (C=O), and 1150–1200 cm^{-1} (CF_3).

B. Trifluoroacetaldehyde Benzoylhydrazone, 1 (X = H; R_F = CF_3). A slurry of 168.6 g (0.72 mol) of 11 (X = H; R_F = CF_3) in 600 ml of thionyl chloride was stirred at room temperature until evolution of gases (HCl + SO_2) has ceased (about 0.5 h). The reaction mixture was concentrated under reduced pressure and the residual solid was recrystallized from methanol to give 104.5 g (67%) of colorless, crystalline solid: ir (KBr) 3370 and 3140 (NH), 1640 (C=N, C=O), and 1230 cm^{-1} (CF_3).

C. 1-Chloro-1-phenyl-4-(trifluoromethyl)azine, 3 (X = H; R_F = CF_3). A solution containing 120 g (0.52 mol) of 1 (X = H; R_F = CF_3) in 250 ml of thionyl chloride was refluxed for 18 h and concentrated under reduced pressure. The residual amber liquid was distilled to give 99.5 g (83%) of amber liquid: bp 70–72 °C (0.5 mm); ir, no apparent C=O or NH; 1000 (C=) and 1180 cm^{-1} (CF_3); NMR ($CDCl_3$) 7.5 (4, CH=) and 8.0 ppm (2, CH=); mass spectrum (70 eV) *m/e* 234 (M^+), 199 (M^+ − Cl, base peak), 165 (M^+ − CF_3), 138 [C_6H_5 − $C(Cl)N^+$], 129 (M^+ − CF_3 − HCl), 104, 103 ($C_6H_5C{\equiv}N^+$), 89 ($C_6H_5C^+$), 69 (CF_3^+).

Anal. Calcd for $C_9H_6ClF_3N_2$: Cl, 15.2. Found: Cl, 15.4.

D. 1,4-Dichloro-1-phenyl-4-(trifluoromethyl)azine, 7 (X = H; R_F = CF_3). Chlorine, 51.2 g (0.72 mol), was passed gradually over a period of 5 h into a solution of 169 g (0.72 mol) of 3 (X = H; R_F = CF_3) in 500 ml of glacial acetic acid. The temperature of the mixture rose to 50 °C. Concentration of the reaction mixture gave an oil that was dissolved in methylene chloride and washed with cold aqueous sodium bicarbonate and then with water. After drying, the solution was concentrated and the residual liquid was distilled to give 135 g (70%) of light red liquid: bp 66–68 °C (0.05 mm); ir (CH_2Cl_2) 1640 (C=N), 1600, 1590, 1500, and 1460 (aromatic), 1220 (CF_3), and 760 cm^{-1} (C–Cl); NMR ($CDCl_3$) 7.4–8.2 ppm (CH=); mass spectrum (70 eV) *m/e* 268 (M^+), 233 (M^+ − Cl), 197 (M^+ − 2HCl), 138 [C_6H_5 − $C(Cl)N^+$], 103 ($C_6H_5C{\equiv}N^+$, base peak), 89 ($C_6H_5C^+$), 69 (CF_3^+), 36 (HCl^+), 20 (HF^+).

Anal. Calcd for $C_9H_5Cl_2F_3N_2$: Cl, 25.4. Found: Cl, 24.8.

When this reaction was carried out in carbon tetrachloride, at 25 °C and 60 h, saturated with chlorine, the yield was 91%.

E. Preparation of 8 (R^1, R^2, X = H; R_F = CF_3). To a solution of 13.5 g (0.05 mol) of 7 (X = H; R_F = CF_3) in 100 ml of ethanol was added at 0–5 °C with stirring 5.1 g (0.15 mol) of 95% hydrazine. The mixture was stirred at room temperature for 3 h, then concentrated under reduced pressure, and the residue was washed with water and filtered. Recrystallization of the residual solid from benzene gave 10.5 g (95%) of yellow crystalline solid; ir (KBr) 3300 (NH), 1700, 1650, and 1585 (C=), and 1150 cm^{-1} (CF_3); NMR (Me_2SO-d_6) 7.2–7.9 (5, m, CH=) and 9.27 and 9.40 ppm (2, NH); mass spectrum (70 eV) *m/e* 228 (M^+).

3-Phenyl-6-(trifluoromethyl)-1,2,4,5-tetrazine, 9 (X = H; R_F = CF_3). A solution of 90 g (0.56 mol) of ferric chloride in 250 ml of water was added to a warm (40 °C) solution of 68 g (0.3 mol) of 8 (R^1, R^2, X = H; R_F = CF_3) in 350 ml of ethanol and 175 ml of water. The mixture was briefly heated to 80 °C, then cooled and filtered. Recrystallization of the filter cake from hexane–ether (1:1) gave 54 g (81%) of red crystalline solid: ir (CH_2Cl_2) 1600, 1450 (C=), 1320, 1200, 1170, and 1140 cm^{-1} (CF_3); NMR ($CDCl_3$) 7.5–7.85 (3, CH=) and 8.8–9.3 ppm (2, CH=).

1,2-Dihydro-3-(2-naphthyl)-6-(trifluoromethyl)-1,2,4,5-tetrazine, 8 (R^1, R^2 = H; X = 3,4-(CH=CHCH=CH); R_F = CF_3). A. Trifluoroacetaldehyde 2-Naphthoylhydrazone, 1 (X = 3,4-(CH=CHCH=CH); R_F = CF_3). A mixture containing 93 g (0.5 mol) of 2-naphthoic acid hydrazide, 116 g (1.0 mol) of trifluoroacetaldehyde hydrate, and 5 drops of concentrated sulfuric acid in 400 ml of ethanol was refluxed for 20 h. The solvent was removed and the residue was washed well with ether, filtered, and dried to give 134 g (100%) of a colorless solid: ir (KBr) 3240 (NH) and 1660 cm^{-1} (C=O); NMR (Me_2SO-d_6) 7.5–8.5 (8, CH=) and 12.55 ppm (1, NH).

B. 1-Chloro-1-(2-naphthyl)-4-(trifluoromethyl)azine, 3 (X = 3,4-(CH=CHCH=CH); R_F = CF_3). A solution of 133 g (0.5 mol) of the hydrazone prepared under A and 10 drops of dimethylformamide in 500 g of thionyl chloride was refluxed for 5 h, and then concentrated under reduced pressure. The residue was dissolved in ether, washed with water, dried, and concentrated. The residual yellow oil, 144 g (100%), crystallized on standing.

Anal. Calcd for $C_{13}H_8ClF_3N_2$: Cl, 12.5. Found: Cl, 12.1.

C. 1,4-Dichloro-1-(2-naphthyl)-4-(trifluoromethyl)azine, 7 (X = 3,4-(CH=CHCH=CH); R_F = CF_3). Chlorine, 40 g (0.56 mol), was introduced into a stirred solution containing 142.5 g (0.50 mol) of the chloroazine prepared under B in 300 ml of carbon tetrachloride. After 2 h, the solvent and excess of chlorine were removed under reduced pressure leaving 159 g (99%) of yellow syrup.

Anal. Calcd for $C_{13}H_7Cl_2F_3N_2$: Cl, 22.3. Found: Cl, 23.2.

D. Preparation of 8 (R^1, R^2 = H; X = 3,4-(CH=CHCH=CH); X = CF_3). To a stirred and cooled (0 °C) solution of 159 g (0.5 mol) of the dichloroazine prepared under C in 300 ml of ethanol was added dropwise (about 20 min) 51 g (1.5 mol) of 95% hydrazine. The reaction

mixture was stirred for 1.5 h at ambient temperature, diluted with water, and filtered. The gummy filter cake was recrystallized from ether to give 78 g (56%) of yellow, crystalline solid: ir (KBr) 3300 (NH) and 1150–1200 cm^{-1} (CF_3); NMR (Me_2SO-d_6) 7.5–8.5 (7, CH=) and 9.67 ppm (2, NH).

Registry No.—**2** (X = H; R_F = CF_3), 59872-52-5; **2** (X = H; R_F = C_3F_7), 736-62-9; **3** (X = H; R_F = CF_3), 54820-21-2; **3** (X = H; R_F = C_2F_5), 54820-24-5; **3** (X = H; R_F = C_3F_7), 59872-53-6; **3** (X = 2-F; R_F = CF_3), 59872-54-7; **3** (X = 4-Cl; R_F = CF_3), 59872-55-8; **3** (X = 4-Cl; R_F = C_2F_5), 59872-56-9; **3** (X = 4-Cl; R_F = C_3F_7), 59872-57-0; **3** (X = 3,4-Cl_2; R_F = CF_3), 59872-58-1; **3** (X = 3-CF_3; R_F = CF_3), 59872-59-2; **3** (X = 3-CH_3; R_F = CF_3), 59872-60-5; **3** (X = 4-CH_3; R_F = CF_3), 59872-61-6; **3** [X = 3,4-$(CH_3)_2$; R_F = CF_3], 59872-62-7; **3** [X = 3,5-$(CH_3)_2$; R_F = CF_3], 59872-63-8; **3** [X = 3,5-$(CH_3)_2$-4-Cl; R_F = CF_3], 59872-64-9; **3** [X = 4-$C(CH_3)_3$; R_F = CF_3], 59872-65-0; **3** (X = 4-NO_2; R_F = CF_3), 59872-66-1; **3** (X = 3,4-CH=CHCH=CH; R_F = CF_3), 59872-67-2; **7** (X = H; R_F = CF_3), 54820-22-3; **7** (X = H; R_F = C_2F_5), 59872-68-3; **7** (X = H; R_F = C_3F_7), 59872-69-4; **7** (X = 2-F; R_F = CF_3), 59872-70-7; **7** (X = 4-Cl; R_F = CF_3), 59872-71-8; **7** (X = 4-Cl; R_F = C_2F_5), 59872-72-9; **7** (X = 4-Cl; R_F = C_3F_7), 59872-73-0; **7** (X = 3,4-Cl_2; R_F = CF_3), 59872-74-1; **7** (X = 3-CF_3; R_F = CF_3), 59872-75-2; **7** (X = 3-CH_3; R_F = CF_3), 59872-76-3; **7** (X = 4-CH_3; R_F = CF_3), 59872-77-4; **7** [X = 3,4-$(CH_3)_2$; R_F = CH_3], 59872-78-5; **7** [X = 3,5-$(CH_3)_2$; R_F = CF_3], 59872-79-6; **7** [X = 3,5-$(CH_3)_2$-4-Cl; R_F = CF_3], 59872-80-9; **7** [X = 4-$C(CH_3)_3$; R_F = CF_3], 59872-81-0; **7** (X = 4-NO_2; R_F = CF_3), 59872-82-1; **7** (X = 3,4-CH=CHCH=CH; R_F = CF_3), 59872-83-2; **10** (X = H), 613-94-5; **10** (X = 2-F), 446-24-2; **10** (X = 4-Cl), 536-40-3; **10** (X = 3-CH_3), 13050-47-0; **10** [X = 3,5-$(CH_3)_2$], 27389-49-7; **10** [X = 4-$C(CH_3)_3$], 43100-38-5; **10** (X = 2-Cl), 5814-05-1; **10** (X = 3,4-Cl_2), 28036-91-1; **10** (X = 4-NO_2), 636-97-5; **10** (X = 3-CF_3), 22227-25-4; **10** [X = 3,5-$(CF_3)_2$], 26107-82-4; **10** (X = 3,4-CH=CHCH=CH), 39627-84-4; hydrazine, 302-01-2; methylhydrazine, 60-34-4; 1,2-dimethylhydrazine, 540-73-8; trifluoroacetaldehyde, 75-90-1; pentafluoropropionaldehyde methyl hemiacetal, 59872-84-3; heptafluorobutyraldehyde ethyl hemiacetal, 356-26-3; trifluoroacetyl chloride, 354-32-5; benzalhydrazone, 5281-18-5; heptafluorobutyric acid hydrazide, 1515-05-5; benzaldehyde, 100-52-7.

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Smiles Rearrangement of 2-Tetrazolylthio-3-aminopyridines

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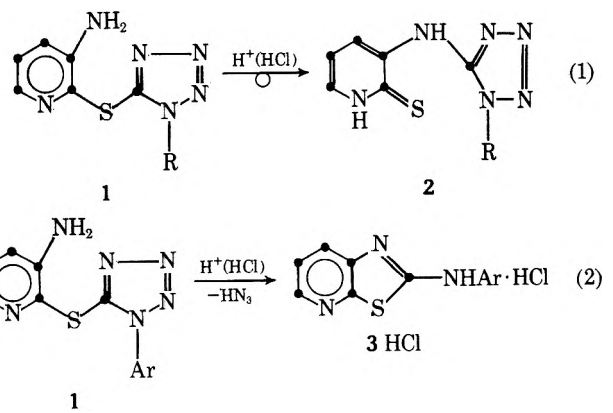
The Smiles rearrangement of 2-tetrazolylthio-3-aminopyridines **1** that contain alkyl and aralkyl substituents on the tetrazole moiety occurs under acidic conditions in refluxing ethanol to yield 2-mercapto-3-tetrazolylaminopyridines **2**. Under the same conditions, hydrazoic acid is eliminated to yield the corresponding 2-anilinothiazolo[5,4-*b*]pyridine **3** when the tetrazole moiety contains an aryl group. The synthesis of the 2-tetrazolylthio-3-aminopyridines and a plausible mechanism for both the Smiles rearrangement and the 2-anilinothiazolo[5,4-*b*]pyridine formation are discussed. Structure proofs for a 2-mercapto-3-tetrazolylaminopyridine and a 2-anilinothiazolo[5,4-*b*]-pyridine are presented. Rearrangements involving a migrating tetrazole ring and a new example of the collapse of a Smiles rearrangement cyclic transition state to form a new heterocyclic ring are demonstrated.

The Smiles rearrangement is an intramolecular nucleophilic aromatic substitution.[1,2] The scope of this reaction increases as more papers describing this rearrangement of a diversity of molecular systems are being published. Smiles recognized that certain diaryl sulfides undergo an intramolecular nucleophilic reorganization under alkaline conditions.[3] Since then, extensive investigations of these isomerizations of diaryl sulfides have been pursued.[1] Later, Maki extended the study of the Smiles rearrangement to phenylpyridyl sulfides[4] and to dipyridyl sulfides.[5] Rodig et al. then showed that this rearrangement of dipyridyl sulfides can occur under acidic as well as basic conditions.[6] This transformation of certain heterocyclic sulfides followed by ring closure has led to some interesting tricyclic ring systems.[7,8] Smiles-type rearrangements in which the migrating aryl ring loses a molecular fragment while the cyclic transition state forms a new ring have been reported.[9,10] The cyclic transition state for this rearrangement, however, has also been trapped as a stable cyclic Meisenheimer complex.[11] Thus far, few examples of Smiles rearrangements of migrating aryl groups containing more than one heteroatom have appeared.[8-10,12-14]

This paper describes the successful acid-promoted Smiles

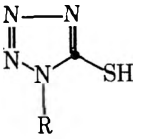


(1)

(2)

rearrangement of 2-tetrazolylthio-3-aminopyridines **1** to the corresponding 2-mercapto-3-tetrazolylaminopyridines **2** (reaction 1). Furthermore, when the R substituent is an aryl group, the elimination of hydrazoic acid occurred under the same acidic conditions to form the corresponding 2-anilinothiazolo[5,4-*b*]pyridine **3** (reaction 2). Previously, an attempted Smiles rearrangement of a phenyltetrazolyl thiohy-

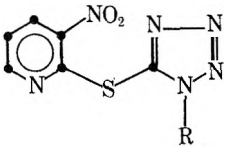
Table I. 1-Substituted 5-Mercaptotetrazoles



Registry no.	R	Yield, %	Mp, °C	Lit. mp, °C
13183-79-4	CH_3	60	121–122	125–126[15]
15217-53-5	C_2H_5	54	45–46	50[15]
42770-71-8	n-C_4H_9	70	37–38	40–41[16]
7624-33-1	CH_2=$CHCH_2$	28	66–67	69[15]
33898-72-5	$C_6H_5CH_2$	48	141–142	144[15]
59888-15-2	$C_6H_5CH_2CH_2$[a]	34	100–101[b]	
14331-22-7	1-Naphthyl	41	148–149	155–160[17]
1544-79-2	4-FC_6H_4	25	155–156	154–155[15]

[a] Gave a satisfactory C, H, N analysis. [b] Crystallized from ethyl ether–ligroin (bp 30–60 °C).

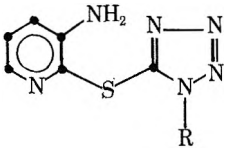
Table II. 2-Tetrazolylthio-3-nitropyridines



Registry no.	R	Yield, %	Mp, °C[a,b]
59888-16-3	CH_3	88	184–185
59888-17-4	C_2H_5	82	163–164
59938-98-6	n-C_4H_9	63	81–82
59888-18-5	CH_2=$CHCH_2$	76	125–126
59888-19-6	$C_6H_5CH_2$	81	138–139
59888-20-9	$C_6H_5CH_2CH_2$	84	111–112
59888-21-0	C_6H_5[c]	60	176–177[d]
59888-22-1	1-Naphthyl	96	200–201[d]
59888-23-2	4-FC_6H_4	70	189–190[d]

[a] All compounds were crystallized at least once from ethanol except the n-butyl compound which was crystallized from ethyl acetate. [b] All compounds gave satisfactory C, H, N analyses except as noted. [c] Anal. Calcd for $C_{12}H_8N_6O_2S$: C, 48.0; H, 2.7; N, 28.0. Found: C, 47.7; H, 2.6; N, 28.5. [d] Decomposed while melting.

Table III. 2-Tetrazolylthio-3-aminopyridines



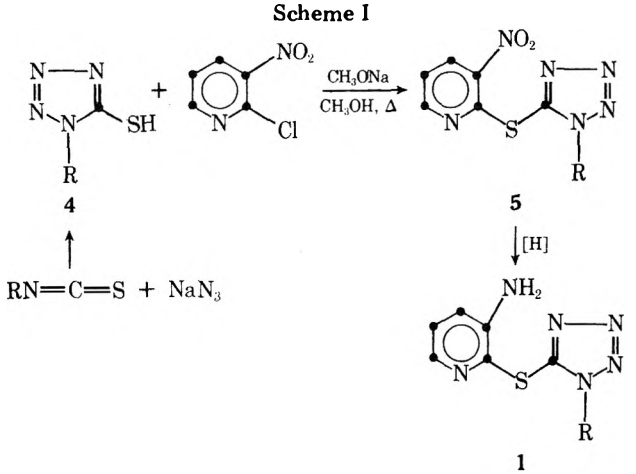
Registry no.	R	Yield, %	Mp, °C	Method[a,b]
59888-24-3	CH_3	54[c]	124–125	A
59888-25-4	C_2H_5	23[d]	77–78	B
59888-26-5	n-C_4H_9[e]	46[d]	108–109	B
59888-27-6	CH_2=$CHCH_2$	55[f]	66–67	A
59888-28-7	$C_6H_5CH_2$	16[d]	140–141	A
59888-29-8	$C_6H_5CH_2CH_2$	55[d]	133–134	A
59888-30-1	C_6H_5	32[c]	135–136[g]	B
59888-31-2	1-Naphthyl	39[d]	149–150[g]	B
59888-32-3	4-FC_6H_4	29[c]	131–133[g]	B

[a] See text. [b] All compounds gave satisfactory C, H, N analyses except as noted. [c] Crystallization from ethanol. [d] Crystallization from ethyl acetate. [e] Anal. Calcd for $C_{10}H_{14}N_6S$: C, 48.0; H, 5.6; N, 33.6. Found: C, 47.5; H, 5.5; N, 33.4. [f] Crystallized from ethyl ether. [g] Decomposed while melting.

drazonate resulted in a cleavage reaction to yield 1-phenyl-5-mercaptotetrazole.[14]

A series of 2-tetrazolylthio-3-aminopyridines was prepared according to Scheme I. The 1-substituted 5-mercaptotetrazoles 4 were prepared by refluxing the appropriately substituted isothiocyanates with excess sodium azide in aqueous solution (Table I). These mercaptotetrazoles, with 1 equiv of sodium methoxide in methanol solution, readily condensed with 2-chloro-3-nitropyridine under reflux conditions to give the corresponding 2-tetrazolylthio-3-nitropyridines 5 as pale yellow crystalline solids (Table II). Reduction of the nitro group to the amino group was achieved either by treatment with tin(II) chloride in concentrated hydrochloric acid (method A) or by catalytic hydrogenation using 10% palladium/charcoal in ethanol (method B). Table III summarizes the 2-tetrazolylthio-3-aminopyridines obtained by both methods.

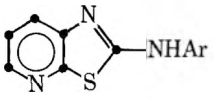
Scheme I



Experimental conditions under which the Smiles rearrangement of 1 occurred were then sought. When 1 (R = C_6H_5) was refluxed in absolute ethanol, only unchanged starting material was recovered. When this 2-tetrazolylthio-3-aminopyridine was refluxed in ethanol that contained a few drops of hydrochloric acid, however, 2-anilinothiazolo[5,4-*b*]pyridine 3 (Ar = C_6H_5) was isolated (as its hydrochloride) instead of the exected 2-mercapto-3-tetrazolylaminopyridine 2 (R = C_6H_5). When 1 (R = C_6H_5) was refluxed in ethanolic potassium hydroxide, the same bicyclic compound was found. The acid-promoted reaction appeared to be much cleaner and gave higher yields of product.

The rest of the compounds in Table III were subjected to the same acidic reaction conditions to determine the generality of this thiazolopyridine synthesis. When R was an aryl group, the corresponding 2-anilinothiazolopyridine 3 was formed (Table IV). When R was an alkyl or an aralkyl group,

Table IV. 2-Anilinothiazolo[5,4-*b*]pyridines[a]



Registry no.	Ar	Yield, %	Mp, °C
59922-51-9	C_6H_5	84[b]	180–181
59888-33-4	4-FC_6H_4	50[c]	209–210
59888-34-5	1-Naphthyl	54[b]	174–175

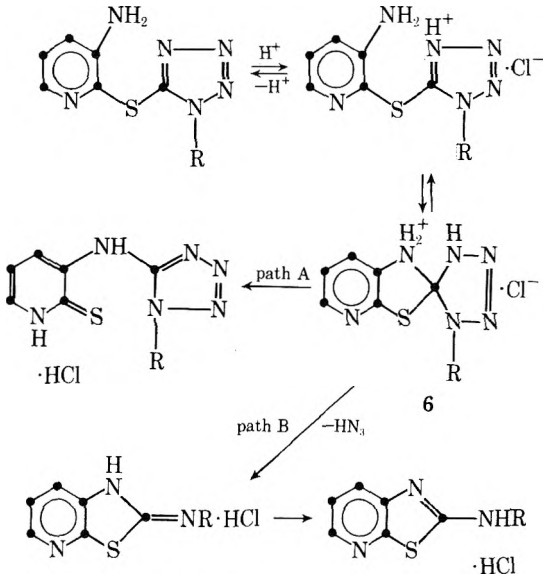
[a] All compounds gave satisfactory C, H, N analyses. [b] Crystallized from ethyl acetate. [c] Crystallized from ethanol.

the normal Smiles rearrangement occurred since the isomeric 2-mercapto-3-tetrazolylaminopyridine **2** was formed (Table V).

Discussion

A reasonable mechanism (Scheme II), involving a common intermediate **6**, may be proposed for the two divergent reac-

Scheme II

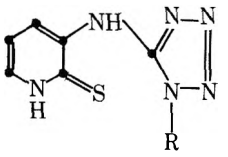


tion pathways exhibited by the 2-tetrazolylthio-3-aminopyridines in refluxing ethanolic hydrochloric acid. The elimination of hydrazoic acid from the proposed spiro intermediate **6** is probably dependent on the ability of the R substituent to stabilize either the free radical or more likely the charged species that results. When R is an alkyl or an aralkyl substituent, the transition state energy required for path B is apparently quite high, and path A, which leads to the normal Smiles rearrangement product, is favored. When R is an aryl substituent, the transition state energy for path B is lowered enough so that this pathway predominates. A diradical species, resulting after the elimination of hydrazoic acid, cannot be definitely excluded at this time.

When **1** (R = C_6H_5) was refluxed in ethanolic hydrochloric acid for 18 h, the hydrochloride salt of **3** was the principal product. The filtrate, after removal of this precipitated **3** HCl, was found by mass spectrometry to consist of additional **3** HCl plus a molecular ion with *m/e* 270. By comparing the fragmentation pattern of this ion with that of pure **1** (R = C_6H_5), an unequivocal assignment of this species to either **1** or **2** could not be made. Whether the normal Smiles rearrangement (**1** → **2**) may occur to a small extent when **1** (R = aryl) is subjected to these acidic reaction conditions is currently being investigated.

When **1** (R = CH_3) was refluxed in ethanolic hydrochloric acid for 18 h, **2** (R = CH_3) was the major product (>95%) found by mass spectrometry.

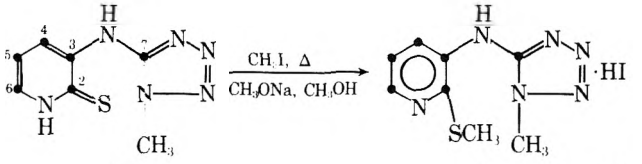
Table V. 2-Mercapto-3-tetrazolylaminopyridines



Registry no.	R	Yield, %	Mp, °C[a,b]
59888-35-6	CH_3	46[c]	217–218
59888-36-7	C_2H_5[d]	9[e]	201–202
59888-37-8	n-C_4H_9	34[e]	190–191
59888-38-9	CH_2=$CHCH_2$	37[e]	191–192
59888-39-0	$C_6H_5CH_2$	50[e]	210–211
59888-40-3	$C_6H_5CH_2CH_2$	60[f]	208–209

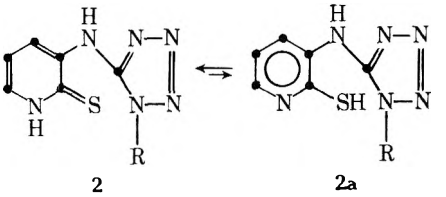
[a] All compounds melted with decomposition. [b] All compounds gave satisfactory C, H, N analyses except as noted. [c] Crystallized from absolute ethanol. [d] Anal. Calcd for $C_8H_{10}N_6S$: C, 43.2; H, 4.5; N, 37.8. Found: C, 43.6; H, 4.6; N, 38.3. [e] Crystallized from ethyl acetate. [f] Crystallized from ethyl acetate–ethanol.

Evidence for the Smiles rearrangement to structure **7** when **1** (R = CH_3) was refluxed in ethanolic hydrochloric acid has been obtained. The 2-mercapto group of **7** was easily converted to its thiomethyl ether **8** with iodomethane and sodium



7 **8** (3)

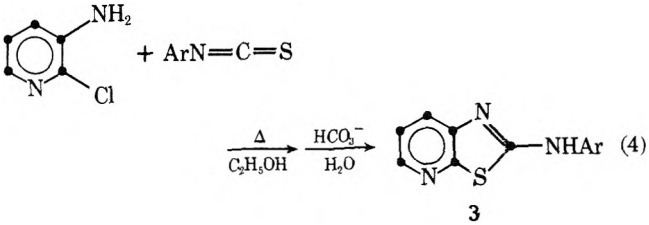
methoxide in refluxing methanol (reaction 3). The thiomethyl carbon of **8** exhibited a ^{13}C NMR resonance at δ 12.828 ppm.[18] Furthermore, the ^{13}C NMR spectrum of **8** showed a resonance for the *N*-methyl carbon at δ 32.549 ppm.[19] The ^{13}C NMR spectrum of **7** showed a resonance at δ 166.166 ppm which was assigned to the 2-thionecarbon atom,[18] while the *N*-methyl carbon resonated at δ 32.369 ppm. The 2-carbon atom resonance of **7** was shifted upfield to δ 153.699 or 153.219 ppm (one value was for C-2, the other for C-7) in compound **8**. These values strongly suggested that **2** exists in the pyridine-2(1*H*)-thione form rather than in the tautomeric thiol form **2a**. For comparative purposes, the ^{13}C NMR spectrum of **1** (R



2 **2a**

= CH_3) revealed a C-2 resonance at δ 149.862 ppm and an *N*-methyl carbon resonance at δ 34.108 ppm.

Thiazolopyridine structure **3** was firmly established by an independent synthesis (reaction 4).[20a,b] The thiazolopyridines **3** (Ar = C_6H_5) obtained by the two different routes (reactions 2 and 4) were identical in all respects.



3

Conclusions

2-Tetrazolylthio-3-aminopyridines 1 that contain alkyl or aralkyl substituents on the tetrazole moiety undergo the normal Smiles rearrangement to 2-mercapto-3-tetrazolylaminopyridines 2 in refluxing ethanolic hydrochloric acid. The 2-tetrazolylthio-3-aminopyridines studied that contain aryl groups on the tetrazole eliminate hydrazoic acid under these acidic conditions to yield 2-anilinothiazolo[5,4-*b*]pyridines 3. These different reaction pathways are probably due to the stability of spiro intermediate 6. The elimination of hydrazoic acid from this spiro intermediate is a new example of a Smiles rearrangement cyclic transition state that loses a molecular fragment to form a new heterocyclic ring. Furthermore, a successful Smiles rearrangement involving a migrating tetrazolyl ring has been demonstrated.

The Smiles rearrangement of other systems that have heterocyclic rings containing at least two heteroatoms is currently being investigated.

Experimental Section[21]

Materials. 1-Phenyl-5-mercapto-1*H*-tetrazole, phenyl isothiocyanate, methyl isothiocyanate, ethyl isothiocyanate, *n*-butyl isothiocyanate, allyl isothiocyanate, benzyl isothiocyanate, 2-phenethyl isothiocyanate, and 1-naphthyl isothiocyanate were Eastman grade compounds. The other compounds, 4-fluorophenyl isothiocyanate, 2-chloro-3-nitropyridine, and 2-chloro-3-aminopyridine, were obtained from the Aldrich Chemical Co.

General Mercaptotetrazole (4) Synthesis[15] Illustrated for 1-(2-Phenethyl)-5-mercapto-1*H*-tetrazole. A stirred aqueous mixture (400 ml) of 2-phenethyl isothiocyanate (40.8 g, 0.250 mol) and sodium azide (24.4 g, 0.375 mol) was refluxed for 6 h. When cool, this aqueous mixture was extracted with two portions of diethyl ether. With ice cooling, the aqueous phase was carefully acidified with concentrated hydrochloric acid, and was then extracted with two portions of diethyl ether. The combined ether extract was washed with distilled water, dried over magnesium sulfate, and the solvent was removed under reduced pressure. The residual colorless solid was crystallized from ethyl ether–ligroin (bp 30–60 °C) to 17.5 g (34%) of colorless crystals. The mercaptotetrazoles described in this paper are presented in Table I.

Representative 2-Tetrazolylthio-3-nitropyridine (5) Synthesis Illustrated for 2-[5-[1-(2-Phenethyl)-1*H*-tetrazolyl]thio]-3-nitropyridine. To a stirred methanol solution (100 ml) of 1-(2-phenethyl)-5-mercapto-1*H*-tetrazole (10.0 g, 0.0485 mol) and sodium methoxide (2.6 g, 0.0485 mol) was added 2-chloro-3-nitropyridine (7.7 g, 0.0485 mol). The resultant stirred solution was refluxed for 16 h and the methanol was removed from the cooled mixture under reduced pressure. The residue was partitioned between chloroform and distilled water, and the chloroform extract was dried over magnesium sulfate. After the solvent was removed under reduced pressure, the residual yellow solid was crystallized from ethanol to yield 13.4 g (84%) of pale yellow prisms. Analytical data for the 2-tetrazolylthio-3-nitropyridines discussed in this paper are summarized in Table II.

Representative 2-Tetrazolylthio-3-aminopyridine (1) Synthesis Illustrated for 2-[5-[1-(2-Phenethyl)-1*H*-tetrazolyl]-thio]-3-aminopyridine (Method A). To a stirred concentrated hydrochloric acid solution (55 ml) of $SnCl_2 \cdot 2H_2O$ (41.3 g, 0.183 mol) was added the corresponding 2-tetrazolylthio-3-nitropyridine (12.0 g, 0.0366 mol) over a 2-h period. The temperature of the stirred mixture was never allowed to exceed 50 °C. This stirred mixture was kept at ambient temperature for 21 h and then was transferred to a 2-l. Erlenmeyer flask. Distilled water (50 ml) and chloroform (200 ml) were added to this mixture, and the resultant slurry was made alkaline with sodium carbonate (1 equiv) and concentrated ammonium hydroxide. After the suspension was removed by filtration through a fritted flask filter, the filtrate was extracted with two portions of chloroform, and the combined chloroform extract was washed with a small amount of distilled water. The chloroform extract was then dried over magnesium sulfate. After the solvent was removed under reduced pressure, the residual solid was crystallized from ethyl acetate to yield 6.0 g (55%) of colorless needles (Table III).

Representative 2-Tetrazolylthio-3-aminopyridine (1) Synthesis Illustrated for 2-[5-(1-Phenyl-1*H*-tetrazolyl)thio]-3-aminopyridine (Method B). A mixture of the corresponding 2-tetrazolylthio-3-nitropyridine (10.5 g, 0.035 mol) and 10% palladium/charcoal (3 g) in ethanol (200 ml) was treated with hydrogen (3 atm) at ambient temperature for 30 h. The catalyst was removed by filtration and the filtrate was concentrated to ca. one-half volume. The precipitated colorless, silky needles were collected and dried, yield 3.0 g, 32% (Table III).

Representative 2-Mercapto-3-tetrazolylaminopyridine (2) or 2-Anilinothiazolo[5,4-*b*]pyridine (3) Synthesis Illustrated for 2-Mercapto-3-[5-[1-(2-Phenethyl)-1*H*-tetrazolyl]amino]-pyridine. A stirred solution of the corresponding 2-tetrazolylthio-3-aminopyridine (4.0 g, 0.0134 mol) and concentrated hydrochloric acid (10 ml) in ethanol (100 ml) was refluxed for 18 h. After the coled solution was concentrated to ca. one-half volume and the concentrate was chilled for 66 h, the precipitated yellow solid was collected by filtration and washed with ethanol. This solid was partitioned between dilute ammonium hydroxide and chloroform. After the chloroform extract was washed with distilled water and the extract was dried over magnesium sulfate, the solvent was removed under reduced pressure. The crystalline residue was crystallized from ethyl acetate–ethanol to yield 2.4 g (60%) of pale yellow prisms. The 2-mercapto-3-tetrazolylaminopyridines and the 2-anilinothiazolo[5,4-*b*]pyridines discussed in this paper are listed respectively in Tables V and IV.

2-Methylthio-3-[5-(1-methyl-1*H*-tetrazolyl)amino]pyridine Hydriodide (8). To a stirred suspension of 2-mercapto-3-[5-(1-methyl-1*H*-tetrazolyl)amino]pyridine (2.1 g, 0.01 mol) and sodium methoxide (0.54 g, 0.01 mol) in methanol (25 ml) was added iodomethane (1.4 g, 0.01 mol). This stirred suspension was refluxed for 66 h and, after cooling, the methanol was removed under reduced pressure. The residue was suspended in hot ethanol and undissolved solid was removed by filtration. A crystalline solid separated from the chilled filtrate: yield 0.3 g (9%); mp 184–185 °C dec; MS *m/e* 222 ($C_8H_{11}IN_6S$ − HI); ^{1}H NMR δ 2.53 (s, 3 H, $-SCH_3$), 3.92 (s, 3 H, NCH_3), 7.22 (dd, $J \simeq 9$, 9 Hz, 1 H), 7.80 (dd, $J \simeq 9$, 2 Hz, 1 H), and 8.37 (dd, $J \simeq 6$, 2 Hz, 1 H); ^{13}C NMR δ 12.828 ($-SCH_3$), 32.549 (NCH_3), 153.219 and 153.699 (C-2, C-7 carbons).

Anal. Calcd for $C_8H_{11}IN_6S$: C, 27.4; H, 3.1; N, 24.0. Found: C, 27.5; H, 3.2; N, 23.9.

Independent Synthesis of 2-Anilinothiazolo[5,4-*b*]pyridine.[20b] A stirred mixture of 2-chloro-3-aminopyridine (2.0 g, 0.016 mol) and phenyl isothiocyanate (2.2 g, 0.016 mol) was refluxed in ethanol (15 ml) for 18 h. After the resultant yellow suspension was chilled, the solid was collected and dried, yield 2.4 g (57%) of the hydrochloride. The base was liberated with aqueous sodium bicarbonate and was crystallized from ethyl acetate, mp 179–180 °C. A mixture melting point with a sample obtained by the elimination of hydrazoic acid from the appropriate 2-tetrazolylthio-3-aminopyridine (vide supra) was undepressed.

Acknowledgment. Stimulating discussions with Professor H. Suschitzky (University of Salford, England) are gratefully acknowledged. D. P. Maier and R. S. Gohlke determined the mass spectra, while T. H. Regan and R. L. Young measured the NMR spectra. The elemental analyses were performed by G. N. Meyer and his staff at the Kodak Research Laboratories.

Registry No.—8, 59888-41-4; phenethyl isothiocyanate, 2257-09-2; 2-chloro-3-nitropyridine, 5470-18-8; 2-chloro-3-aminopyridine, 6298-19-7; phenyl isothiocyanate, 103-72-0.

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(21) Mass spectra were determined on a Hitachi Perkin-Elmer RMS-4 spectrometer. ^{1}H NMR spectra were measured with an A-60 Varian Associates or with a Perkin-Elmer R-32 (90 MHz) NMR spectrometer. The ^{13}C spectra were measured on a Brüker Model HX-90 (22.63 MHz) NMR spectrometer. Me_2SO-d_6 was used as the solvent and Me_4Si as the internal standard for all NMR spectra determinations. All of the compounds in the tables gave satisfactory mass and ^{1}H NMR spectra.

Oxidations by Thionyl Chloride. 8. A Convenient Synthesis of Benzo[*b*]thiophenes from Carboxylic Acids and Ketones[1,2]

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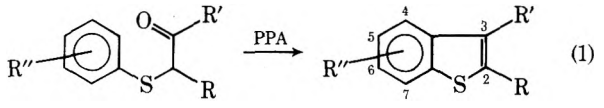
Benzo[*b*]thiophenes are prepared in one step from cinnamic acids, hydrocinnamic acids, or certain ketones plus thionyl chloride and pyridine. Para-substituted cinnamic acids gave rise to benzo[*b*]thiophenes in 41–69% yields together with α-chlorocinnamic acid derivatives. 3-Substituted 3-phenylpropanoic acids gave 3-aryl- or -alkyl benzo[*b*]thiophenes in 77% (3-H) to 16% (3-CH_3) yield; in the latter case, uncyclized sulfenyl chloride was also found. Ketones of the type $PhCH_2CH_2COR$ gave benzo[*b*]thiophenes in 52% (R = Ph) and 68% (R = *tert*-butyl) yields. An alternative two-step synthesis from 3-substituted 3-phenylpropanoic acids via cyclization of sulfenyl chloride **11** furnished benzo[*b*]thiophenes in 61% (3-H) and 66% (3-CH_3) yields, but only 2-chloro-1-phenylinden-3-one (**13**) and 1-oxoindeno[2,3-*d*]benzo[*b*]thiophene (**14**) in 12 and 63% yields, respectively (3-Ph). The indenones were also prepared by Friedel–Crafts cyclization of the sulfenyl chlorides derived from cinnamic acids.

Among a number of synthetic methods known[3,4] for the preparation of benzo[*b*]thiophenes, cyclodehydration of aryl sulfides (for example, arylthio acetones, eq 1) is the most



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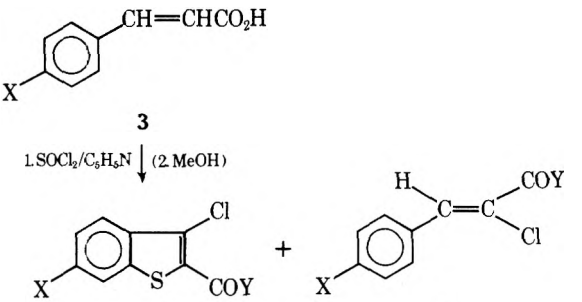
common and widely practiced method. This method unambiguously affords 5- and 7-substituted benzo[*b*]thiophenes from para- and ortho-substituted phenyl sulfides, respectively, but mixtures of 4- and 6-substituted benzo[*b*]thiophenes result from meta-substituted starting materials. In this method, preparation of starting materials usually requires a several-step sequence of reactions.

On the other hand, as evident from a previous paper,[5] if the reaction of thionyl chloride with cinnamic acids or 3-arylpropanoic acids can be generally applied, it would furnish 4- and 6-substituted benzo[*b*]thiophenes from ortho- and para-substituted starting materials, respectively, and 5- and 7-substituted benzo[*b*]thiophenes from meta-substituted starting materials. Thus the reaction would offer a convenient method for the preparation of benzo[*b*]thiophenes not only by supplementing the cyclodehydration methods, but also by being a one-step synthesis. We now describe a synthetic application of the thionyl chloride reaction to the preparation of benzo[*b*]thiophenes.[6]

Results and Discussion

Direct Synthesis of Benzo[*b*]thiophenes from Cinnamic Acids, 3-Phenylpropanoic Acids, and Certain 3-Phenyl 1-Substituted 2-Propanones. As described in a preceding paper,[5] cinnamic acid (**3a**) furnished the benzo[*b*]-thiophene **4a** in 69% yield when treated with an excess of thionyl chloride and a catalytic amount of pyridine at 120–125 °C.

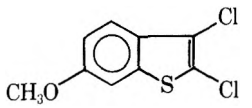


Yield of **4**, %

a, X = H; Y = Cl	69
b, X = CH_3; Y = Cl	60.7
c, X = CH_3; Y = OCH_3	40.5
d, X = OCH_3; Y = OCH_3	47.5
e, X = NO_2; Y = OCH_3	46

Similarly *p*-methylcinnamic acid (**3b**) gave benzo[*b*]thiophene **4b** in 60.7% yield and the methyl ester **4c** in 40.5% yield. *p*-Methoxy- (**3d**) and *p*-nitrocinnamic acids (**3e**) furnished benzo[*b*]thiophenes **4d** and **4e** in 47.5 and 46% yield, respectively. The structures of **4a–e** were assigned by spectroscopic data and elemental analyses. No attempt was made to maximize the yields of these products.

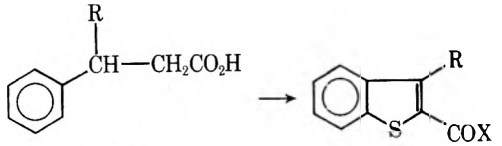
Common by-products for the reactions of the acid **3a** to **3d** were α-chlorocinnamic acid derivatives **5**. The reaction of **3e** did not give **5e**, but methyl α,β-dichloro-4-nitrocinnamate and methyl 4-nitrobenzoate as minor products. Another minor product from the reaction of **3d** was the benzo[*b*]thiophene **6** which, isolated in 0.7% yield, showed no carbonyl absorption



6

in the infrared spectrum. The mass spectrum [*m/e* 232 (100), 234 (68.5), 236 (15.7%)] indicated the presence of two chlorine atoms. Thus the structure was assigned as indicated by analogy to other 2,3-dichlorobenzo[*b*]thiophenes[5] isolated from the reaction of other cinnamic acids.

The reaction of 3-phenylpropanoic acid (**7a**) previously afforded the benzo[*b*]thiophene **4a** in 31.6% yield.[7] The yield of **4a** was improved to 77% when **7a** was treated with 5 equiv of thionyl chloride and 0.12 equiv of pyridine at 140–150 °C for 6 h. Under similar conditions 3,3-diphenylpropanoic acid (**7b**) gave after hydrolysis the known[8] benzo[*b*]thiophene **8b** in 65% yield.

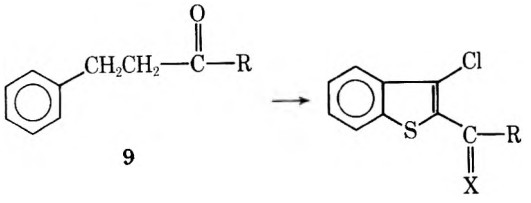


7 8

a, R = H; X = OH
b, R = C_6H_5; X = OH
c, R = CH_3; X = Cl
d, R = CH_3; X = OCH_3

The reaction of 3-phenylbutanoic acid **7c**, however, furnished the corresponding benzo[*b*]thiophene **8c** in only 16% yield. Prolonged heating did not improve the yield. Most of the material remained as uncyclized sulfenyl chloride. This slow cyclization was an important clue to the cyclization mechanism.[5] These two examples show that 3-alkyl or aryl substituted benzo[*b*]thiophenes can be prepared by a one-step reaction from 3-phenylpropanoic acids. In contrast, a previous synthesis of **8b** required several steps.[8]

Apart from carboxylic acids, ketones of the type $ArCHRCH_2COR'$, in which the R′ group has no enolizable hydrogens, can also form benzo[*b*]thiophenes when treated with an excess of thionyl chloride and a catalytic amount of pyridine. We examined the reaction with two such ketones, benzylacetophenone (**9a**) and benzylpinacolone (**9b**). Thus treatment of **9a** with 3 equiv of thionyl chloride and a catalytic amount of pyridine at 125–130 °C for 3 h furnished, after separation on an alumina column, the benzo[*b*]thiophene **10a**



9 10

	Yield, %
a, R = C_6H_5; X = O	52
b, R = $C(CH_3)_3$; X = O	53.5
c, R = $C(CH_3)_3$; X = Cl_2	14.3

in 52% yield. Similarly, treatment of **9b** with 4 equiv of thionyl chloride afforded the benzo[*b*]thiophenes **10b** and **10c** in 53.5 and 14.3% yield, respectively.

The structure of **10a** was assigned by elemental analysis and spectroscopic data: the NMR spectrum showed only aromatic hydrogens at δ 7.92 and 7.55 (multiplets); the infrared spectrum revealed carbonyl absorption at 1634 cm^{-1}, a position which is virtually identical with that (1631 cm^{-1}) reported[9] for 2-benzoylbenzo[*b*]thiophene; and the mass spectral fragmentation pattern correlated well with that of **4a**.

The structure of **10b** was assigned by analogy to **10a**. Compound **10c** showed no carbonyl absorption in the ir spectrum, but the NMR spectrum [δ 7.95–7.32 (m, 4 H), 1.36 (s, 9 H)] was almost identical with that [δ 7.96–7.34 (m, 4 H), 1.33 (s, 9 H)] of **10b**. Furthermore, **10c** was obtained in 15.5% yield by independent treatment of **10b** with thionyl chloride and pyridine at 130 °c for 1 h. Indeed, some examples of such chlorination of ketones by thionyl chloride to form *gem*-dichlorides are known,[10] and the reaction appears to be especially facile in the presence of a tertiary amine.

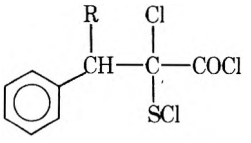
The yields of benzo[*b*]thiophenes obtained from ketones in the above examples are moderate and comparable to those of benzo[*b*]thiophenes obtained from cinnamic acids and 3-phenylpropanoic acids. Unfortunately, however, with the exception of **8b** and **8c**, the benzo[*b*]thiophenes thus far obtained have been those possessing a chlorine substituent at the 3 position. Because this constitutes a limit on the scope of our synthesis, we developed a method that has more general applicability to the synthesis of benzo[*b*]thiophenes.

Synthesis of Benzo[*b*]thiophenes by Friedel–Crafts Reaction of Sulfenyl Chlorides. Alkyl sulfenyl chlorides, when treated with aromatic compounds and aluminum chloride, are known[11] to afford aryl alkyl sulfides. Thus it was proposed that application of the reaction to a sulfenyl chloride such as **11** would effect, intramolecularly, the formation of benzo[*b*]thiophenes which have no chlorine substituent at the 3 position.

Sulfenyl chlorides of the type **11** can be easily prepared by treating carboxylic acids **7** with thionyl chloride and pyridine. Typically the α-methylene group of a saturated carboxylic acid is completely oxidized by treatment of the acid with 7 equiv of thionyl chloride and 0.12 equiv of pyridine at reflux (bath temperature 95 °C) for 21 h. The product mixture, after excess thionyl chloride and pyridine hydrochloride are removed, usually consists of approximately 80% sulfenyl chloride which can be used for cyclization without further purification.

Thus, sulfenyl chloride **11a**, prepared from **7a**, was treated with 1 equiv of aluminum chloride in methylene chloride at 5–10 °C and hydrolyzed to yield benzo[*b*]thiophene-2-carboxylic acid (**8a**) in 61– yield. Similarly sulfenyl chloride **11c**, prepared from **7c**, was treated with 2.2 equiv of aluminum chloride in methylene chloride at 0–3 °C, esterified with methanol, and separated by column chromatography to furnish the known[12] benzo[*b*]thiophene **8d** in 66% yield. Thus the yield was improved by 50% from the direct method.

Sulfenyl chloride **11c** was shown to be a 1:1 mixture of di-

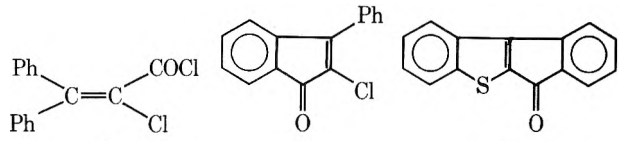


11a, R = H
b, R = C_6H_5
c, R = CH_3
d, R = Cl

astereomers by NMR spectroscopy [δ 7.28 (m, aromatic), 4.02 and 3.91 (two sets of q, methine), 1.58 and 1.47 (two sets of d, methyl protons)].

Treatment of **7b** with thionyl chloride and pyridine under the conditions for forming sulfenyl chloride furnished a mixture which was composed of 72% of **11b** and 28% of a mixture assumed to be the olefin **12** and the acid chloride of **8b**. Treatment of the entire mixture with an excess of aluminum chloride in methylene chloride at 0–3 °C afforded a red solid mixture which upon separation on an alumina column furnished the known[13] indenones **13** as orange and **14** as red crystals in 12 and 63% yield, respectively. Indenone **13** would presumably be formed by cyclization of **12**, while **14** would be

formed by cyclization of both **11b** and the acid chloride of **8b**.



12 **13** **14**

Compounds **13** (33%) and **14** (35%) were also obtained by Friedel–Crafts reaction on the mixture formed when β-phenylcinnamic acid was treated with thionyl chloride and pyridine. Another example which unexpectedly produced **14** was the Friedel–Crafts reaction of sulfenyl chloride **11d** with benzene. Thus treatment of **11d**, prepared[5] from cinnamic acid, with 2.2 equiv of aluminum chloride in benzene at 10–15 °C afforded, after separation on an alumina column, **14** in 42% yield.

Such application of Friedel–Crafts reactions on sulfenyl chlorides as shown by the above examples makes the reaction of thionyl chloride a more useful and general method for the synthesis of benzo[b]thiophenes than direct formation of the compounds. Furthermore, certain indenones may also be prepared. This is just another example of sulfenyl chlorides, prepared by the oxidation of carboxylic acids or certain ketones with thionyl chloride, having high potential as synthetic intermediates.

Experimental Section

Thionyl chloride (Matheson Coleman and Bell) was distilled from triphenyl phosphite;[15] the fraction boiling over the range 75.5–76.5 °C was used. Alumina used for chromatographic columns was Woelm neutral unless otherwise specified. Infrared spectra were recorded with a Perkin-Elmer Model 137 spectrophotometer with a sodium chloride prism; solid samples were taken as potassium bromide pellets and liquid samples were taken as neat films. Mass spectra were processed by Mr. C. R. Weissenberger with an AEI MS-9 mass spectrometer[16] at 70 eV. The nuclear magnetic resonance spectra were taken on a Varian Model A-60 spectrometer, using tetramethylsilane as the internal reference and carbon tetrachloride as solvent unless otherwise specified. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are corrected. Boiling points are uncorrected. Elemental analyses were performed by Chemalytics, Inc., Tempe, Ariz., and Galbraith Laboratories, Knoxville, Tenn.

General Procedure for the Reaction of Thionyl Chloride with Para-Substituted Cinnamic Acids. To a mixture of 0.02 mol of a para-substituted cinnamic acid and 0.2 ml of pyridine was added one-third of 8.4 g (0.07 mol) of thionyl chloride; the mixture then was heated to 140 °C. The rest of the thionyl chloride was added at such a rate that the temperature did not drop below 135 °C. The mixture was heated at the same temperature for an additional 30 min, cooled, esterified with excess methanol and benzene, and separated on an alumina column.

3-Chloro-2-chlorocarbonyl-6-methylbenzo[b]thiophene (4b). *p*-Methylcinnamic acid (**3b**, 8.10 g, 0.05 mol) was treated with 21.0 g (0.175 mol) of thionyl chloride and 0.5 ml of pyridine under the conditions of the general procedure. The mixture (acid chlorides) was dissolved in hot hexanes (300 ml) and decanted to separate pyridine hydrochloride. Four recrystallizations from the solution afforded 7.11 g of **4b**, mp 123.5–125.7 °C. The residue was distilled to yield 3.30 g of yellow oil, bp 93–100 °C (0.3–0.4 mm), and undistilled material which upon recrystallization from hexanes furnished 0.33 g of **4b**. Thus the total yield of **4b** was 7.44 g (60.7%). A pure sample of **4b** appeared as pale yellow needles: mp 124.7–125.7 °C; ir 5.67 (C=O), 6.25 (C=C), 6.80, 8.54, 10.96, 12.29, and 14.04 μ; mass spectrum *m/e* 246, 244 (M^+), 211, 209 (base, - Cl), and 181 (- COCl).

The distillate was a mixture of *p*-methylcinnamoyl chloride (10%) and α-chloro-*p*-methylcinnamoyl chloride (**5b**, 23%) as shown by NMR spectroscopy after esterification with methanol.

3-Chloro-2-methoxycarbonyl-6-methylbenzo[b]thiophene (4c). *p*-Methylcinnamic acid (**3b**, 3.24 g, 0.02 mol) was treated with thionyl chloride and pyridine and then with absolute methanol (70 ml) and benzene (30 ml) under the conditions of the general procedure. The product was separated on a column (100 g of activity grade II alumina) by eluting with petroleum ether into 23 fractions (50–100 ml each) and petroleum ether–ether (5:1) into 3 fractions (150 ml each). Fractions 1–3 gave approximately 0.1 g of sulfur. The material obtained by combining fractions 4–23 (total 3.55 g) was recrystallized from ligroin to furnish 1.85 g of **4c**, mp 84.5–89 °C. The residue after separation of **4c** was distilled to yield 1.00 g of a mixture (2:3) of methyl *p*-methylcinnamate and methyl α-chloro-*p*-methylcinnamate. The mixture was confirmed by the comparison of the NMR spectrum with those of authentic samples. The distillation residue was crystallized from ligroin to yield 0.1 g more of **4c**, mp 84–88 °C. Thus the total yield of **4c** was 1.95 g (40.5%). Further recrystallization from ligroin afforded an analytical sample of **4c** as white plates: mp 88.5–89 °C; NMR ca. δ 7.79 (d, H_4, J = 8.5 Hz), 7.45 (finely splitted singlet, H_7), 7.16 (finely splitted doublet, H_5, J = 8.5 Hz), 3.89 (s, OCH_3), and 2.45 (s, CH_3); ir 5.93 (C=O), 6.70, 7.67, 7.86, 8.06 (C–O), and 9.20 μ; mass spectrum *m/e* 242, 240 (M^+), 211, 209 (base, $-OCH_3$), 181 ($-CO_2CH_3$), and 145 ($-CO_2CH_3$, -HCl).

Anal. Calcd for $C_{11}H_9ClO_2S$: C, 54.89; H, 3.77; Cl, 14.73; S, 13.32. Found: C, 54.73; H, 3.51; Cl, 14.96; S, 13.31.

3-Chloro-6-methoxy-2-methoxycarbonylbenzo[b]thiophene (4d). *p*-Methoxycinnamic acid (**3d**, 3.56 g, 0.02 mol) was treated with thionyl chloride and pyridine, followed by methanol (100 ml) and benzene (40 ml) under the conditions of the general procedure. The product was separated on a column (150 g of activity grade III alumina) by eluting with petroleum ether–benzene (1:1) into 13 fractions (50 ml each). Fractions 3–6 (3.57 g) were mixtures which were combined and fractionally crystallized from ethanol to furnish 2.185 g (42.5%) of **4d**, mp 131–138 °C, and 0.92 g (20%) of **5d**, mp 65–70 °C.

The latter compound was recrystallized from ethanol–water to afford white, fine crystals: mp 67–70 °C; NMR δ 7.70 (s, one vinyl), 7.67 and 6.86 (AB quartet, four aromatic hydrogens, J = 9.0 Hz), and 3.79 and 3.76 (2 s, 2 OCH_3); ir 5.85 (C=O) and 6.23 μ (C=C); mass spectrum *m/e* 228 (M + 2) and 226 (M^+).

An analytical sample of **4d** was obtained by further recrystallization from ethanol, giving white, fine needles: mp 138–138.5 °C; NMR ($CDCl_3$) ca. δ 7.72 (d, H_4, J = 8.5 Hz), 7.13 (d, H_7, J = 2.0 Hz), 7.01 (dd, H_5, J = 8.5, 2.0 Hz), and 3.91 and 3.85 (2 s, 2 OCH_3); ir 5.93 (C=O) and 6.25 μ (C=C); mass spectrum *m/e* 258, 256 (M^+, base), 227, 225 ($-OCH_3$), and 197 ($-CO_2CH_3$).

Anal. Calcd for $C_{11}H_9ClO_3S$: C, 51.47; H, 3.53; Cl, 13.81; S, 12.49. Found: C, 51.26; H, 3.39; Cl, 13.71; S, 12.67.

The compound **4d** was separated in 47.5% yield when the product after esterification was directly crystallized from ethanol.

2,3-Dichloro-6-methoxybenzo[b]thiophene (6). *p*-Methoxycinnamic acid (**3d**) was treated with thionyl chloride and pyridine followed by methanol and benzene under the conditions of the general procedure. Separation of the product was effected on a column (activity grade II alumina) by eluting with petroleum ether into eight fractions (50 ml each). Fractions 4–6 upon recrystallization from 95% ethanol afforded 34 mg (0.7%) of **6**: mp 70–73 °C; ir 6.23 (C=C), 6.78, 7.89 (C–O), and 12.07 μ; mass spectrum *m/e* 236 (M + 4), 234 (M + 2), 232 (M^+, base), 221, 219, 217 ($-CH_3$), 191, and 189 ($-COCH_3$).

3-Chloro-2-methoxycarbonyl-6-nitrobenzo[b]thiophene (4e). Under the conditions of the general procedure *p*-nitrocinnamic acid (**3e**, 3.86 g, 0.02 mol) was treated with thionyl chloride and pyridine, followed by absolute methanol (100 ml). The product was chromatographed on an alumina (activity grade III, 150 g) column by eluting with benzene into 20 fractions (50 ml each for fractions 1–7, 125 ml for 8–12, 250 ml for 13–17, and 500 ml for 18–20). Recrystallization of the fractions 4–20 (2.51 g) from ethyl acetate gave rise to 1.93 g of **4e**, mp 214.5–215.5 °C. Fractions 2 and 3 (1.52 g) were fractionally crystallized to furnish 0.57 g of **4e**, mp 214–215 °C, and 0.88 g of a mixture. Thus the separated yield of **4e** was 2.50 g (46%). Further recrystallization of **4e** from ethyl acetate afforded an analytical sample as yellow prisms: mp 216–216.5 °C; NMR ($CDCl_3$) ca. δ 8.72 (d, H_7, J = 2.0 Hz), 8.29 (dd, H_5, J = 9.0, 2.0 Hz), 8.07 (d, H_4, J = 9.0 Hz), and 4.00 (s, OCH_3); ir 5.93 (C=O) and 8.03 μ (C–O); mass spectrum *m/e* 273, 271 (M^+, base), 241 (-NO), 242, 240 ($-OCH_3$), 196, 194 ($-NO_2$, $-OCH_3$), and 166 ($-NO_2$, $-CO_2CH_3$).

Anal. Calcd for $C_{10}H_6ClNO_4S$: C, 44.21; H, 2.23; Cl, 13.05; N, 5.16; S, 11.80. Found: C, 44.52; H, 2.08; Cl, 13.33; N, 5.18; S, 11.87.

The residue after separation of **4e** from fractions 2 and 3 was sublimed at 60 °C (0.3 mm) for 3 h to yield 0.10 g of methyl *p*-nitrobenzoate: mp 91.5–92.5 °C (lit.[17] 96 °C); NMR δ 8.20 (s, four aromatic) and 3.97 (s, three methyl hydrogens); ir 5.80 (C=O), 6.23, and 7.85 μ; mass spectrum *m/e* 181 (M^+) and 150 (base, $-OCH_3$).

3-Chloro-2-chlorocarbonylbenzo[b]thiophene (4a). To a mixture of 7.5 g (0.05 mol) of **7a** and 0.5 ml of pyridine was added ca. ⅕ of 30 g (0.25 mol) of thionyl chloride. The mixture was heated to 140 °C, and the rest of the thionyl chloride was added at a rate as not to drop the temperature below 135 °C (2 h). The mixture was then

heated at 140–150 °C for an additional 4 h. After cooling, the mixture was dissolved in 200 ml of hot hexane and decanted from pyridine hydrochloride. Crystallization of the solution furnished 8.94 g (77%) of benzo[*b*]thiophene **4a**, mp 114.5–115.5 °C. The remaining material (1.80 g) consisted of **5a** and other unidentified products as shown by NMR spectroscopy.

3-Phenylbenzo[*b*]thiophene-2-carboxylic Acid (8b). To a mixture of 3,3-diphenylpropanoic acid (**7b**, 2.00 g, 0.009 mol) and 0.9 ml of pyridine was added 1 equiv (ca. 0.8 ml) of thionyl chloride. The mixture was heated to 150–160 °C, more thionyl chloride (ca. 2.3 ml, total amount of thionyl chloride was 5.0 g) was added over a period of 1 h, and this mixture was heated at this temperature for an additional 2 h. The product was added dropwise with stirring to a mixture of 10 ml of water, 1 ml of concentrated hydrochloric acid, and 15 ml of tetrahydrofuran, and heated at reflux for 3 h. The tetrahydrofuran was distilled and the residue was cooled, extracted with ether, washed with saturated sodium chloride solution, dried ($MgSO_4$), and concentrated to yield white solid. The solid was crystallized from benzene to yield 1.49 g (65%) of white powder, mp 197–199 °C. Recrystallization from the same solvent gave pure acid **8b**, mp 199–200 °C (lit.[8] mp 199–200 °C).

2-Chlorocarbonyl-3-methylbenzo[*b*]thiophene (8c). To a mixture of 4.11 g (0.025 mol) of **7c** and 0.25 ml of pyridine was added 12.0 g (0.1 mol) of thionyl chloride at 120–130 °C over a period of 2 h. The mixture was heated at this temperature for an additional 6 h. After excess thionyl chloride and pyridine hydrochloride were removed, the resulting black mixture was crystallized from *n*-hexane to yield 0.85 g (16%) of crude **8c**, mp 90–105 °C (lit.[12] mp 108–109 °C), and 0.20 g of sulfur. Most of the remaining material was the sulfenyl chloride **11c** as shown by infrared spectroscopy.

2-Benzoyl-3-chlorobenzo[*b*]thiophene (10a). To a mixture of 2.10 g (0.01 mol) of **9a** and 0.1 ml of pyridine was added 3.6 g (0.03 mol) of thionyl chloride at 125 °C over a period of 30 min. The mixture was heated at 125–130 °C for an additional 2.5 h, cooled, taken up into ether, successively washed with water and with saturated sodium chloride solution, dried ($MgSO_4$), and evaporated to yield 2.70 g of a very viscous oil. The oil was placed on an alumina (activity grade I, 70 g) column and eluted with light petroleum ether–ether (5:1) into ten fractions (100–200 ml each). Fractions 3–7 (950 ml, 1.51 g) were recrystallized from hexane to yield 1.42 g (52%) of the benzo[*b*]thiophene **10a**, mp 77–78 °C. Further recrystallization from hexane afforded an analytical sample: mp 78 °C; NMR δ 7.92 (m) and 7.55 (m); ir 6.12 μ.

Anal. Calcd for $C_{15}H_9ClOS$: C, 66.05; H. 3.33; Cl, 13.00; S, 11.76. Found: C, 65.92; H, 3.34; Cl, 13.01; S, 11.62.

Benzylpinacolone (9b). Benzalpinacolone[18] (18.8 g, 0.01 mol, mp 42–43 °C) was hydrogenated with atmospheric hydrogen over 10% palladium on charcoal (1 g) in 80 ml of ethyl acetate at room temperature till uptake (2450 ml) ceased. After removal of the catalyst and the solvent the product was distilled to yield 18.61 g (97.8%) of benzylpinacolone **9b**: bp 60–62 °C (0.007 mm); ir 3.34 and 5.86 μ (C=O); NMR δ 7.12 (s, 5 H), 2.77 (m, 4 H), and 1.04 (s, 9 H).

Reaction of Thionyl Chloride with Benzylpinacolone (9b). To a mixture of 3.60 g (0.019 mol) of **9b** and 0.19 ml of pyridine was added 9.1 g (0.076 mol) of thionyl chloride at 120–130 °C over a period of 50 min. Approximately three-quarters of the thionyl chloride was rapidly consumed (30 min). The mixture was heated at this temperature for an additional 1 h, cooled, and directly chromatographed on an alumina (activity grade III, 180 g) column. The column was eluted with light petroleum ether into 15 fractions (50 ml each for fractions 1–5 and 100 ml each for 6–15). Recrystallization of fractions 1 and 2 from 95% ethanol afforded 30 mg of sulfur and 835 mg (14.3%) of benzo[*b*]-thiophene **10c**: mp 107–108 °C; ir no carbonyl absorption; NMR δ 7.95–7.32 (m, 4 H) and 1.36 (s, 9 H).

Anal. Calcd for $C_{13}H_{13}Cl_3S$: C, 50.75; H. 4.26; Cl, 34.57; S, 10.42. Found: C, 50.53; H, 4.21; Cl, 34.36; S, 10.57.

The residue of fraction 2 and fractions 3–6 furnished 2.67 g (53.5%) of benzo[*b*]thiophene **10b**: bp 103–107 °C (0.1 mm); ir 3.32 (C–H) and 5.91 μ (C=O); NMR δ 7.96–7.34 (m, 4 H) and 1.33 (s, 9 H); mass spectrum *m/e* 254 (M + 2), 252 (M^+), 197, 195 ($-C_4H_9$, base), 167 ($-COC_4H_9$), 132 ($-COC_4H_9$, –Cl), 123 ($-COC_4H_9$, –CS), 57 (C_4H_9), and 41 (C_3H_5).

Fractions 7–15 were small amounts of mixtures.

Reaction of Thionyl Chloride with 3-Chloro-2-benzo[*b*]thienyl *tert*-Butyl Ketone (10b). To a mixture of 0.5 g (2 mmol) of **10b** and 3 drops of pyridine was added portionwise at 130 °C 1 g of thionyl chloride. The mixture was heated over a period of 1 h, excess thionyl chloride was removed, and the residue was separated on an alumina (activity grade I, 30 g) column by eluting with petroleum ether into seven fractions (50 ml each). Fractions 2–6 afforded 95 mg (15.5%) of **10c**, mp 104–106 °C. Recrystallization from 95% ethanol gave mp 107–108 °C. The infrared spectrum was identical with that obtained previously.

General Procedure for the Preparation of Sulfenyl Chlorides Used for Friedel–Crafts Reaction. A carboxylic acid was treated with 7 equiv of thionyl chloride and 0.12 equiv of pyridine at moderate reflux (bath temperature 95 °C) for 21 h. After excess thionyl chloride was removed, the product was dissolved in hexane or benzene and filtered to remove pyridine hydrochloride. Solvent was removed by distillation under vacuum, and purity of the sulfenyl chloride was determined by NMR spectroscopy. The sulfenyl chloride was used for cyclization without further purification.

Benzo[*b*]thiophene-2-carboxylic Acid (8a). To a vigorously stirred solution of 5.0 g (0.015 mol) of sulfenyl chloride **11a** (purity 80%) in 150 ml of dry methylene chloride was added portionwise over a 10-min period 2.0 g (0.015 mol) of aluminum chloride (powder). The solution, which turned from yellow to red and then to black, was stirred at 5–10 °C for an additional 1 h and decomposed with 60 ml of 3 N hydrochloric acid. The layers were separated, and the aqueous layer was extracted with methylene chloride (2 × 50 ml). The combined methylene chloride solution was washed with saturated sodium chloride solution and solvent was evaporated to furnish crude 2-chlorocarbonylbenzo[*b*]thiophene. The crude product was hydrolyzed by heating with an ethanol (50 ml)/20% sodium hydroxide (15 ml) solution. After the solution was extracted with ether, the aqueous solution was acidified with 30 ml of 10% hydrochloric acid and extracted with ether (3 × 50 ml). The latter ethereal solution was dried ($CaCl_2$) and evaporated to yield 3.2 g of crude acid which upon crystallization from benzene–ethyl acetate afforded 0.8 g of **8a**, mp 236–238 °C. Second and third crystallizations gave 0.83 g of less pure product, mp 215–230 °C; total yield of **8a** was 1.63 g (61%).

2-Chloro-2-chlorosulfenyl-3-phenylbutanoyl Chloride (11c). Compound **11c**, prepared from 3-phenylbutanoic acid according to the general procedure, was shown to be a mixture (1:1) of diastereomers and 90% pure by NMR spectroscopy: δ 7.28 (m, aromatic), 4.02 and 3.91 (pair of quartets, methine), and 1.58 and 1.47 (pair of doublets, methyl hydrogens). The infrared spectrum of **11c** showed characteristic carbonyl absorptions at 5.60 and 5.70 μ (shoulder).

3-Methyl-2-methoxycarbonylbenzo[*b*]thiophene (8d). To a vigorously stirred solution of 3.3 g (0.0105 mol) of sulfenyl chloride **11c** in 150 ml of dry methylene chloride was added at 1–3 °C over a period of 30 min 3.07 g (0.023 mol) of aluminum chloride (powder). The mixture was stirred at room temperature for another 30 min and then decomposed with 60 ml of 6 N hydrochloric acid. The layers were separated, and the aqueous layer was extracted with methylene chloride (100 ml). The combined methylene chloride solution was dried ($CaCl_2$) and concentrated to yield 2.50 g of crude acid chloride **8c** which was then treated with absolute methanol (100 ml) at reflux for 1 h. A small amount of insoluble tar was separated and discarded. The methanolic solution was concentrated to yield 2.0 g of crude ester **8d**. The crude product was separated on a silica gel (activity grade I, 50 g) column by eluting with 600 ml of petroleum ether–ether (10:1) to furnish 1.43 g (66%) of **8d**, mp 99–102 °C. Recrystallization of this product from ligroin gave slightly yellow needles: mp 102.5–103 °C (lit.[12] mp 101–102 °C); ir 5.89 (C=O), 6.60, 7.01, 7.94, and 8.10 μ (C–O); NMR ($CDCl_3$) δ 7.71 and 7.33 (m, aromatic), 3.86 (s, OCH_3), and 2.68 (s, CH_3).

2-Chloro-2-chlorosulfenyl-3,3-diphenylpropanoyl Chloride (11b). 3,3-Diphenylpropanoic acid (**7b**, mp 154.5–155.5 °C) was treated with thionyl chloride and pyridine under the conditions of the general procedure to furnish a yellow, viscous oil which contained sulfenyl chloride **11b** (72%) and presumably olefin **12** and the acid chloride of **8b** as minor components. The NMR spectrum showed absorptions at δ 7.30 (m) due to aromatic hydrogens of all the components and δ 5.25 (s) due to the methine hydrogen of **11b**.

1-Oxoindeno[2,3-*d*]benzo[*b*]thiophene (14) and 2-Chloro-1-phenylinden-3-one (13). The yellow oil (2.66 g) obtained by treatment of 3,3-diphenylpropanoic acid with thionyl chloride and pyridine was treated with aluminum chloride in methylene chloride under the same conditions described for the preparation of **8d**. The crude product (2.05 g) thus obtained was separated on an alumina (activity grade I, 50 g) column. Elution with 400 ml of petroleum ether–ether (10:1) gave rise to 0.22 g (12%) of **13**. Further elution with 300 ml of benzene furnished 1.16 g (63%, based on **7b**) of **14** as red crystals, mp 185–190 °C. Recrystallization from ligroin–benzene afforded **14** as red needles: mp 194.5–196 °C (lit.[14] 195–196 °C); ir identical with the reported[14] spectrum; NMR ($CDCl_3$) δ 8.03–7.06 (m); mass spectrum *m/e* 237 (M + 1), 236 (M^+, base), and 208 (–CO); mol wt (mass spectrum) for $^{12}C_{15}{}^{1}H_8{}^{16}O^{32}S$ 236.02949 (calcd, 236.02958).

Anal. Calcd for $C_{15}H_8OS$: C, 76.24; H, 3.41; S, 13.56. Found: C, 75.82; H, 3.29; S, 13.44.

Crude **13** was recrystallized from 95% ethanol to afford orange plates: mp 100.5–101 °C (lit.[13] mp 99–100 °C, orange plates from benzene); ir 5.83 (C=O) and 6.26 μ (C=C); NMR ($CDCl_3$) δ 7.61–7.20 (m); mass spectrum *m/e* 242 (M + 2), 240 (M^+, base), 205 (-Cl), 177 (-Cl, -CO), 176, and 88.

Reaction of Thionyl Chloride with β-Phenylcinnamic Acid. A mixture of 4.48 g (0.02 mol) of β-phenylcinnamic acid,[19] 0.2 ml of pyridine, and 16.8 g (0.14 mol) of thionyl chloride was heated at reflux (bath temperature 95–100 °C) for 48 h. The infrared spectra recorded after 24 and 48 h were shown to be identical. After excess thionyl chloride was removed by distillation the residue was dissolved in 50 ml of hexanes, filtered to remove pyridine hydrochloride, and concentrated to yield 4.38 g of yellow oil, a mixture of acid chlorides. The mixture (100 mg) in 2 ml of acetone was heated with 2 ml of 2 N sodium hydroxide solution on a steam bath till acetone was evaporated and a clear aqueous solution was formed. Acidification with dilute hydrochloric acid afforded, after filtration and drying, 80 mg of a mixture of acids. Recrystallization of the mixture from benzene gave 25 mg of **8b**, mp 198–200 °C (lit.[8] mp 199–200 °C), the infrared spectrum being identical with that of **8b** previously obtained. Further crystallization of the mother liquor from ligroin afforded 50 mg of crude 2-chloro-3-phenylpropenoic acid, mp 127–136 °C (lit[13] mp 136 °C).

To a stirred solution of half (2.20 g) of the above mixture of acid chlorides in 150 ml of dry methylene chloride was added portionwise at 2–3 °C approximately 2.2 equiv (2.26 g) of aluminum chloride. The temperature of the solution (dark green) was raised and maintained at 25 °C for 30 min. The solution was decomposed with 50 ml of 6 N hydrochloric acid, the layers were separated, and the aqueous layer was extracted with methylene chloride (50 ml). The combined methylene chloride solution was successively washed with water, saturated sodium bicarbonate solution, and saturated salt solution, dried ($MgSO_4$), and evaporated to yield 1.90 g of a mixture of solids. The mixture was separated on an alumina (activity grade III, 70 g) column. Elution with 50 ml of petroleum ether–ether (10:1) gave after recrystallization from ligroin, 0.80 g (33.2%) of ketone **13**, mp 99–101 °C (lit.[13] mp 99–100 °C). Further elution with benzene (500 ml) afforded, after recrystallization from ligroin, 0.82 g (35%) of **14** as red needles, mp 194–196 °C (lit.[14] mp 195–196 °C); the infrared spectra of **13** and **14** were identical with those of authentic samples.

Benzo[*b*]thiophene 14 from Sulfenyl Chloride 11d. To 1.83 g (5 mmol) of **11d** (83% purity) in 30 ml of dry benzene was added 1.5 g (1.1 mmol) of aluminum chloride portionwise at 10 °C. The mixture was stirred at 10–15 °C for 1 h and decomposed with 6 N hydrochloric acid (50 ml), and the layers were separated. The aqueous layer was extracted with benzene (50 ml × 2). The combined benzene layers were successively washed with water and saturated sodium bicarbonate solution, dried ($MgSO_4$), and concentrated to yield 1.73 g of dark red solid. The solid was placed on a column containing 50 g of alumina (activity grade II) and eluted with petroleum ether–benzene (5:1) into seven fractions (50 ml each) and with a 1:1 mixture of the same solvent pair into ten more fractions (75–100 ml each). Recrystallization of fractions 5–9 from methanol afforded a total of 0.5 g (42%) of **14** as red needles, mp 195–196 °C. Mixture melting point with an authentic sample showed no depression, and the infrared spectrum was identical with that of an authentic sample.

Registry No.—**3b**, 103-26-4; **3d**, 830-09-1; **3e**, 619-89-6; **4a**, 21815-91-8; **4b**, 34576-87-9; **4c**, 59812-34-9; **4d**, 59812-35-0; **4e**, 59812-36-1; **6**, 59812-37-2; **7a**, 501-52-0; **7b**, 606-83-7; **7c**, 4593-90-2; **8a**, 6314-28-9; **8b**, 29491-86-9; **8c**, 41280-76-6; **8d**, 3133-81-1; **9a**, 1083-30-3; **9b**, 5195-24-4; **10a**, 59812-38-3; **10b**, 59812-39-4; **10c**, 59812-40-7; **11a**, 21815-89-4; **11c**, 39252-25-0; **11d**, 39252-24-9; **13**, 13093-22-6; **14**, 23339-77-7; thionyl chloride, 7719-09-7; methyl *p*-nitrobenzoate, 619-50-1; benzalpinacolone, 538-44-3; 2-chlorocarbonylbenzo[*b*]thiophene, 39827-11-7; 3-phenylbutanoic acid, 4593-90-2; β-phenylcinnamic acid, 606-84-8; 2-chloro-3-phenylpropenoic acid, 1727-39-5.

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Trapping of Thiaziridinimines with Imines and Nitriles

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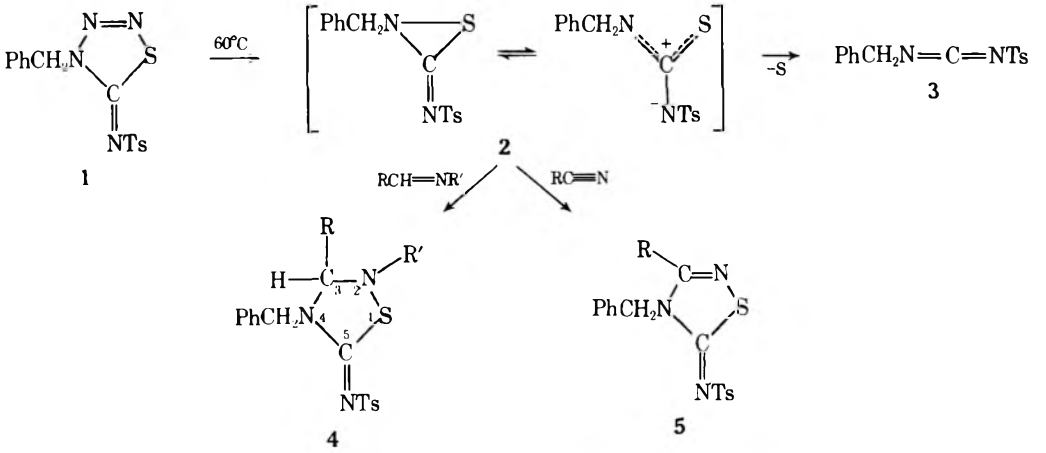
Thermolysis of 4-benzyl-5-tosylimino-1,2,3,4-thiatriazoline (**1**) at 60–70 °C in the presence of imines and nitriles furnished respectively 5-tosylimino-1,2,4-thiadiazolidines (**4**) and 5-tosylimino-1,2,4-thiadiazolines (**5**) in good yields. Structure elucidation was based on spectral analyses and, in the case of **5**, on an independent synthesis and a crystal structure analysis. The ^{13}C NMR spectra of the new heterocycles are discussed by comparison with several model compounds.

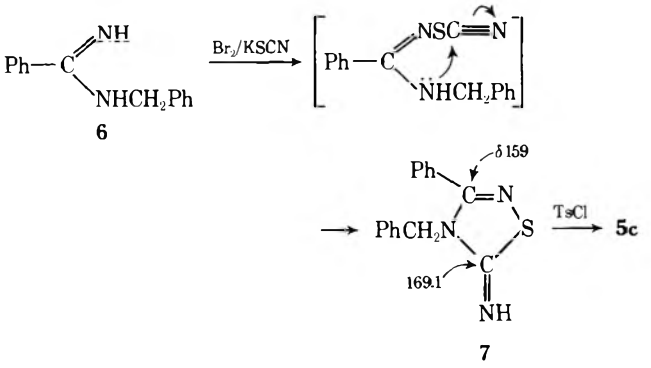
Thiaziridinimines or their ring-opened 1,3-dipolar species (e.g., **2**) have never been isolated, but their existence during the thermal conversion of 4-alkyl-5-sulfonyl-1,2,3,4-thiatriazolines into sulfonylcarbodiimides (e.g., **1** → **3**), has recently been demonstrated.[1,2] Thus, intermediate **2** was efficiently trapped with suitable olefins, acetylenes, keto-stabi-



lized phosphorus ylides, and heterocumulenes. Further work on the reactivity of thiaziridinimines has now shown that intermediate **2** can also be intercepted with imines and nitriles to give adducts **4** and **5**, respectively, having a 1,2,4-thiadiazoli(di)ne ring structure.

Cycloadducts. When imines were heated in CCl_4 with an equimolar amount of 4-benzyl-5-tosylimino-1,2,3,4-thiatriazoline (**1**) at 60–70 °C for 2 h, compounds **4a–d** were obtained in fairly good yields. Nitriles, however, proved to be less efficient for trapping intermediate **2**, but good results were obtained by using them as solvent in our experiments. The results are summarized in Table I.

The reaction products are characterized by ir (C=NTs absorptions at 1545–1550 cm^{-1} for **4a–d** and at 1500–1530 cm^{-1} for **5a–d**), ^1H NMR, mass spectra, microanalyses, and the following independent synthesis. *N*-Benzylbenzamidine (**6**), prepared by the $AlCl_3$ catalyzed reaction of benzonitrile with benzylamine,[3] was treated with bromine and potassium thiocyanate.[4] The resulting 3-phenyl-4-benzyl-5-imino-1,2,4-thiadiazoline (**7**) was then tosylated in the presence of

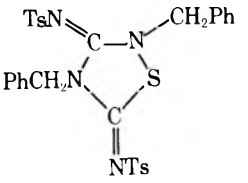


pyridine to give **5c**, identical in all respects with the reaction product of **1** and benzonitrile. Treatment of **5c** with KOH in ethanol at reflux temperature furnished *N*-benzyl-*N'*-tosylurea and benzoic acid in high yields.

Table I. 5-Tosylimino-1,2,4-thiadiazoli(di)nes

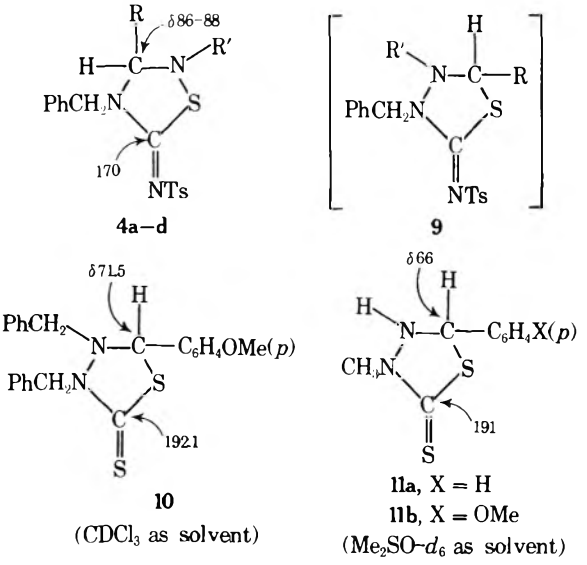
Compd	R	R'	Yield, %	Mp, °C
4a	C_6H_5	CH_3	77	155
4b	C_6H_5	*p*-ClC_6H_4	80	129–131
4c	*p*-$NO_2C_6H_4$	*p*-ClC_6H_4	47	189–192
4d	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	68	151–154
5a	CH_3		25	135–136.5
5b	$C_6H_5CH_2$		62	137–139
5c	C_6H_5		68	163–165
5d	*p*-$MeOC_6H_4$		77	143–144

Our method provides a new entry into the 1,2,4-thiadiazole ring system.[5] The only side product isolated in many reactions with nitriles was 2,4-dibenzyl-3,5-ditosylimino-1,2,4-thiadiazolidine (**8**), mp 221–223 °C. This compound, which resulted



from cycloaddition of **2** to **3** during the thermolysis reaction, has also been obtained in small amounts in previous trapping experiments.[1]

^{13}C NMR Analysis of Thiadiazoli(di)nes. The compounds **4a–d** showed the expected C=NTs ring carbon absorption at δ 170 ppm in the ^{13}C NMR spectra.[1] The other ring carbon atom resonated at δ 87 ppm pointing to a C–N(N) grouping in the adduct. Indeed, if addition had occurred in the reverse sense to give **9**, the C–N(S) ring carbon would be expected to absorb at higher field (ca. δ 70 ppm). This is shown for the model compounds **10**, **11a**, and **11b** from the literature.[6,7] For compounds **5a–d** the situation is less straightforward. In order to distinguish between the C_3 and C_5 ring carbon absorptions, undecoupled NMR spectra were analyzed. The C_3 absorptions (at δ 156–157 ppm) were then broadened owing to multiple coupling, whereas the C_5 absorptions (at δ 177 ppm) were split into a triplet, only coupled with the benzyl protons. In addition, selective decoupling of the methyl hydrogens in **5a** enabled us to locate the C_3 carbon absorption



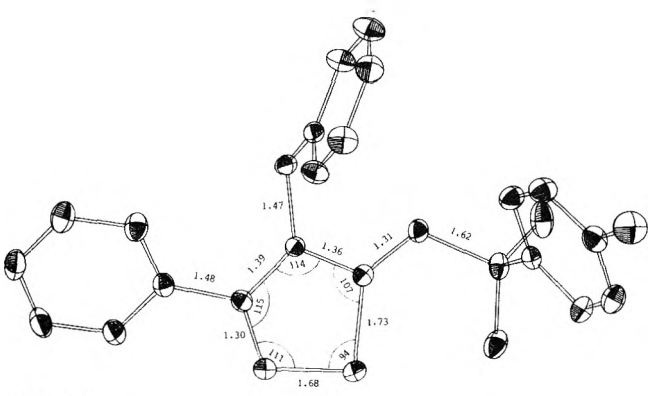
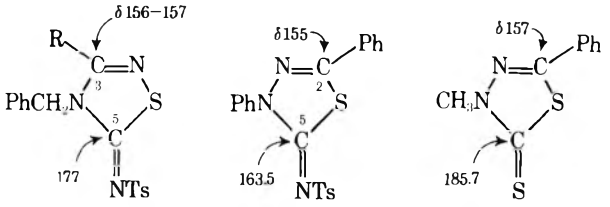


Figure 1.

at δ 155.6 ppm. For an interpretation of these results, we have made use of model compounds **12** and **13,** having a reversed structure about the endocyclic C=N moiety.[7,8] From the absorption values for C_3 in structures **5a–d** and C_2 in structures **12** and **13,** we are forced to the conclusion that differentiation between the two isomeric rings cannot be made on the basis of the chemical shift of the nitrile carbon atom in the adducts, as it was done for the imine adducts. In addition, the absorption values for the C_5 ring atoms in **5a–d** occurred at unusually low field (δ 177 ppm) compared with similar systems such as **1** (δ 166 ppm), **12** (δ 163.5 ppm), and others.[1] The difference between **5a–d** and **12,** however, parallels the larger



5a–d **12** (CDCl₃ as solvent) **13** (CDCl₃ as solvent)

difference observed very recently[9] for the C_5 absorptions in the aromatic systems isothiazole (δ 148.6 ppm) and thiazole (δ 118.8 ppm).

X-Ray Analysis of 5c. In view of the unusual ^{13}C NMR results and the knowledge that related ring systems are prone to undergo rearrangements,[10] we have determined the crystal structure of compound **5c,** confirming that it is in fact 3-phenyl-4-benzyl-5-tosylimino-1,2,4-thiadiazoline. The bond lengths (Table II and Figure 1) are as would be expected for a thiadiazoline structure. All rings are planar within 0.01 Å and the atoms directly linked to the thiadiazoline ring also lie within 0.01 Å of the ring plane.

Experimental Section

Ir spectra were recorded with a Perkin-Elmer Model 521 spectrometer, mass spectra with an AEI MS-12 instrument, and ^1H NMR spectra with a JOEL MH-100 or Varian XL-100 spectrometer. For ^{13}C NMR spectra, the XL-100 apparatus was equipped with a device for pulsed Fourier transform operation. All chemical shifts are relative to Me_4Si.

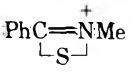
1-Benzyl-5-tosylimino-1,2,3,4-thiatriazoline (**1**), mp 101–103 °C dec, was prepared as reported[1] by the reaction of benzyl azide with 1 equiv of tosyl isothiocyanate in CCl_4 at room temperature.

2-(*p*-Methoxyphenyl)-3,4-dibenzyl-1,3,4-thiadiazolidine-5-thione (**10**), mp 136–137 °C, was obtained by heating *N,N'*-dibenzylhydrazine with anisaldehyde and carbon disulfide according to the method of Huisgen et al.[6] Samples of model compounds **11a, 11b,** and **13** were kindly provided by Dr. Petersen of the Bayer industry, Leverkusen, Germany.[7]

2,4-Diphenyl-5-tosylimino-1,3,4-thiadiazoline (**12**), mp 189–191 °C, was prepared by treatment of *N*-(α-chlorobenzylidene)-*N'*-phenylhydrazine with thiourea as reported,[8] followed by tosylation of the resulting 2,4-diphenyl-5-imino-1,3,4-thiadiazoline (**12,** H instead of Ts) in the presence of triethylamine.

Synthesis of 5-Tosylimino-1,2,4-thiadiazolidines 4a–d. Equimolar amounts (0.01 mol) of **1** and imine were heated in CCl_4 (25–50 ml) at 60–70 °C for 2 h and the reaction residue was then worked up by crystallization from methanol.

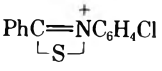
Compound **4a:** mp 155 °C; ^1H NMR ($CDCl_3$) δ 2.50 (s, 3 H, *p*-CH_3), 2.55 (s, 3 H, CH_3N), 3.85 (d, 1 H, benzyl proton, J = 15 Hz), 5.15 (s, 1 H, ring CH), 5.45 (d, 1 H, J = 15 Hz), 6.9–7.5 (m, 14 H), and 7.9 (d, 2 H); mass spectrum (70 eV) *m/e* (rel intensity) 437 (29, $M^{\cdot+}$), 360 (4, $M^{\cdot+}$ − Ph), 346 (1, $M^{\cdot+}$ − Tol), 224 (2, $M^{\cdot+}$ − TsNCS), 151 (74, $M^{\cdot+}$ − TsNCNBz), 150 (100, i), 119 (12), 118 (26), 91 (93).



i

Anal. Calcd for $C_{23}H_{23}N_3O_2S_2$ (437): C, 63.13; H, 5.26; N, 9.61; O, 7.32; S, 14.65. Found: C, 63.15; H, 5.25; N, 9.50; O, 7.35; S, 14.50.

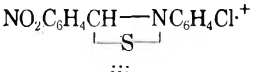
Compound **4b:** mp 129–131 °C; ^1H NMR ($CDCl_3$) δ 3.53 (s, 3 H, *p*-CH_3), 3.87 (d, 1 H, J = 15 Hz), 5.37 (d, 1 H, J = 15 Hz), 5.75 (s, 1 H, ring CH), 6.7–7.47 (m, 16 H), and 7.9 (d, 2 H); mass spectrum *m/e* (rel intensity) 533 (5, $M^{\cdot+}$), 320 (10, $M^{\cdot+}$ − TsNCS), 319 (6, $M^{\cdot+}$ − TsNCS − H), 247 (18, $M^{\cdot+}$ − TsNCNBz), 246 (22, ii), 216 (18), 215 (16), 214 (22), 194 (4), 180 (5), 165 (4), 155 (20), 91 (100).



ii

Anal. Calcd for $C_{28}H_{24}ClN_3O_2S_2$ (533): C, 62.98; H, 4.50; N, 7.87. Found: C, 63.16; H, 4.79; N, 7.69.

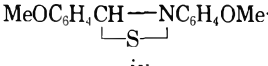
Compound **4c:** mp 189–192 °C; ^1H NMR δ 2.51 (s, 3 H, *p*-CH_3), 5.3 (s, 1 H, ring CH), 5.41 (d, 1 H, J = 15 Hz), 5.98 (d, 1 H, J = 15 Hz), 6.74–7.67 (m, 13 H), 7.92 (d, 2 H), and 8.3 (d, 2 H); mass spectrum *m/e* (rel intensity) 578 (5, $M^{\cdot+}$), 365 (3, $M^{\cdot+}$ − TsNCS), 292 (7, iii), 286 (4), 275 (6), 260 (14), 245 (3), 239 (3), 230 (4), 229 (4), 213 (6), 91 (100).



iii

Anal. Calcd for $C_{28}H_{23}ClN_4O_4S_2$ (578): C, 58.08; H, 3.98; N, 9.68. Found: C, 58.16; H, 4.13; N, 9.50.

Compound **4d:** mp 151–154 °C; ^1H NMR ($CDCl_3$) δ 2.51 (s, 3 H, *p*-CH_3), 3.78 (s, 3 H, *p*-OCH_3), 3.87 (s, 3 H, *p*-OCH_3), 3.90 (d, 1 H, J = 15 Hz), 5.39 (d, 1 H, J = 15 Hz), 5.64 (s, 1 H, ring CH), 6.58–7.44 (m, 15 H), and 7.92 (d, 2 H); mass spectrum *m/e* (rel intensity) 559 (2, $M^{\cdot+}$), 346 (1, $M^{\cdot+}$ − TsNCS), 286 (6), 273 (3, iv), 241 (89), 226 (78), 171 (2), 156 (4), 155 (40), 91 (100).



iv

Anal. Calcd for $C_{30}H_{29}N_3O_4S_2$ (559): C, 64.40; H, 7.51. Found: C, 64.74; H, 7.38.

Synthesis of 5-Tosylimino-1,2,4-thiadiazolines 5a–d. Compound **1** (0.01 mol) was thermolyzed at 60 °C in the presence of a 20-fold excess of nitrile (tenfold in the case of *p*-$MeOC_6H_4CN$) for 2 h and then heated at 80 °C for another 1 h. The excess of nitrile was distilled off in vacuo and the oily residue was crystallized from dry ether (40 ml) to give solids which in all cases except for **5d** were contaminated with 8 (15–30% by NMR). Purification was performed by fractional crystallization from methanol or in the case of **5a** by chromatography on a silica gel column using EtOAc–$CHCl_3$ (1:20 ratio) as the eluent.

Compound **5a:** mp 135–136.5 °C; ^1H NMR ($CDCl_3$) δ 2.31 (s, 3 H, CH_3), 2.39 (s, 3 H, *p*-CH_3), 5.12 (s, 2 H, benzyl CH_2), 6.97–7.32 (m, 7 H), and 7.74 (d, 2 H); mass spectrum *m/e* (rel intensity) 361 (4), 360 (7), 359 (39, $M^{\cdot+}$), 206 (4), 205 (10), 204 (85, $M^{\cdot+}$ − Tos), 181 (3), 163 (21), 91 (100).

Anal. Calcd for $C_{17}H_{17}N_3O_2S_2$ (359): C, 56.83; H, 4.73; N, 11.70. Found: C, 56.76; H, 4.92; N, 11.72.

Compound **5b:** mp 137–139 °C; ^1H NMR ($CDCl_3$) δ 2.38 (s, 3 H, *p*-CH_3), 3.90 (s, 2 H, benzyl CH_2), 5.00 (s, 2 H, benzyl CH_2), 6.80–7.36 (m, 12 H), and 7.70 (d, 2 H); mass spectrum *m/e* (rel intensity) 437 (4), 436 (8), 435 (36, $M^{\cdot+}$), 346 (2), 345 (4), 344 (25, $M^{\cdot+}$ − Bz), 282 (3), 281 (9), 280 (47, $M^{\cdot+}$ − Ts), 190 (1), 189 (2, $M^{\cdot+}$ − Ts − Bz), 181 (1), 91 (100).

Anal. Calcd for M·+ (determined by high-resolution exact-mass measurements): 435.1074. Found: 435.10323.

Compound **5c**: mp 163–165 °C; ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3 H, p-CH_3), 5.13 (s, 2 H, benzyl CH_2), 6.68–7.60 (m, 12 H), and 7.73 (d, 2 H); mass spectrum *m/e* (rel intensity) 423 (4), 422 (8), 421 (36, M·+), 356 (2, M·+ − SO_2 − H), 268 (3), 267 (10), 266 (62, M·+ − Ts), 234 (1, M·+ − Ts − S), 181 (2), 165 (2), 91 (100).

Anal. Calcd for $C_{22}H_{19}N_3O_2S_2$ (421): C, 62.71; H, 4.51; N, 9.98. Found: C, 62.66; H, 4.70; N, 10.05.

Compound **5d**: mp 143–144 °C; ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3 H, p-CH_3), 3.79 (s, 3 H, p-OCH_3), 5.13 (s, 2 H, benzyl CH_2), 6.73–7.36 (m, 11 H), and 7.69 (d, 2 H); mass spectrum *m/e* (rel intensity) 453 (4), 452 (8), 451 (38, M·+), 386 (2, M·+ − SO_2 − H), 298 (3), 297 (8), 296 (48, M·+ − Ts), 264 (1, M·+ − Ts − S), 190 (2), 91 (100).

Anal. Calcd for $C_{23}H_{21}N_3O_3S_2$ (451): C, 61.20; H, 4.66; N, 9.31. Found: C, 61.20; H, 4.95; N, 9.19.

For the independent synthesis of **5c**, the procedure of Goerdeler et al.[4] was utilized to prepare **7**. This compound (1.3 g) was dissolved in dry benzene (20 ml) containing 0.4 g of pyridine. An equimolar amount of tosyl chloride (0.95 g) was added dropwise with stirring and the reaction mixture was left overnight at room temperature. The precipitate (PyHCl) was filtered off and the filtrate was evaporated in vacuo to give a solid (**5c**, 76%) which was crystallized from methanol.

Basic Hydrolysis of 5c. Compound **5c** (4.2 g) was dissolved in a 2.4 M solution of KOH in ethanol (200 ml). The solution was refluxed for 2 h, then poured into ice–water (100 ml) and acidified with 2 N aqueous hydrochloric acid. The precipitate (*N*-benzyl-*N'*-tosylurea)[1] was isolated and dried in vacuo at 70 °C, yield 92%, mp 178–180 °C. The mother liquor was extracted twice with ether and the extracts were dried and then evaporated to give benzoic acid in 82% yield.

Crystal Structure Determination of 5c. Crystal data: $C_{22}H_{19}N_3O_2S_2$ (421.54); monoclinic, a = 10.049 (5), b = 19.985 (3), c = 10.526 (5) Å, β = 107.97 (3), d_m = 1.39 (1) g cm^{-3}, d_c (Z = 4) = 1.392 g cm^{-3}, μ (Cu Kα) = 25.17 cm^{-1}. Systematic absences $0k0$ for k odd and $h0l$ for l odd establish the space group as $P2_1/c$. Intensity data from a crystal 0.33 × 0.30 × 0.14 mm were collected for a quarter of reciprocal space out to 2θ = 144° with graphite-monochromatized Cu Kα radiation (λ = 1.54178 Å) using a Nonius CAD-4 diffractometer in the θ–2θ mode; 3941 independent reflections were measured of which 883 had $I < 3\sigma(I)$ and were considered as unobserved. The data were corrected for absorption by the method of Busing and Levy[11] and for the usual geometric and polarization factors. The structure was solved by direct methods. Hydrogen atoms were located by the use of difference Fourier techniques. The structure was refined with individual isotropic temperature factors for the hydrogen atoms, individual anisotropic temperature factors for all other atoms, and correction for anomalous dispersion of the sulfur atoms to a final R value of 3.9% for the observed reflections. All computations were carried out using the local version of the x-ray 72 program system.[12]

Acknowledgment. The support of this work by the F.K.F.O. (Belgium) is gratefully acknowledged. We are also indebted to Professor G. Evrard of the Facultés Universitaires de Namur for carrying out the crystallographic intensity measurements, and to Dr. R. Albert, A. Willocx, and L. Huybrechts for their assistance in this work.

Registry No.—**1**, 42770-61-6; **4a**, 59938-44-2; **4b**, 59938-45-3; **4c**, 59938-46-4; **4d**, 59938-47-5; **5a**, 59938-48-6; **5b**, 59938-49-7; **5c**, 59938-50-0; **5d**, 59938-51-1; **7**, 59938-52-2; RCH=NR' (R = C_6H_5; R' = CH_3), 622-29-7; RCH=NR' (R = C_6H_5; R' = p-ClC_6H_4), 15383-71-8; RCH=NR' (R = p-$NO_2C_6H_4$; R' = p-ClC_6H_4), 25105-56-0; RCH=NR' (R = R' = p-$MeOC_6H_4$), 3261-60-7; RC=N (R = CH_3), 75-05-7; RC≡N (R = $C_6H_5CH_2$), 140-29-4; RC≡N (R = C_6H_5), 100-47-0; RC≡N (R = p-$MeOC_6H_4$), 874-90-8.

Supplementary Material Available. Tables of bond lengths and angles and final atomic parameters of **5c** (5 pages). Ordering information is given on any current masthead page.

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Structure and Reactions of an Unusual Thionyl Chloride Oxidation Product. 9-Chloroacridinium 2-Chloro-1-(chlorosulfinyl)-2-oxoethylide

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9-Oxo-10-acridanacetic acid (1) reacts with thionyl chloride to give the title compound (2) in 95% yield. The structure 2 is established by x-ray crystallography. Exposures of 2 to amines, alcohols, and water indicate that, in addition to the anticipated reactions at the acyl chloride and the 9-chloroacridinium sites, the chlorosulfinyl group of 2 is readily cleaved. Controlled methanolysis, however, afforded the unstable thioamide *S*-oxide 7. Pyrolysis of 2 leads to 9-chloroacridine.

9-Oxo-10-acridanacetic acid (1)[1] is a compound of some interest as an antiviral agent.[2] In the course of derivatization of **1**, we attempted to prepare the corresponding acid chloride by treatment with thionyl chloride. The dissolution of **1** ($C_{15}H_{11}NO_3$) with thionyl chloride in refluxing 1,2-dimethoxyethane was followed by crystallization of a copious amount (95%) of crimson red prisms, mp 206–208 °C, having the elemental composition of $C_{15}H_8Cl_3NO_2S$. We wish to record the structure (**2**) and reactions of this unusual intermediate.

The structure **2** has been determined by x-ray crystallography, details of which are described below. A stereodrawing

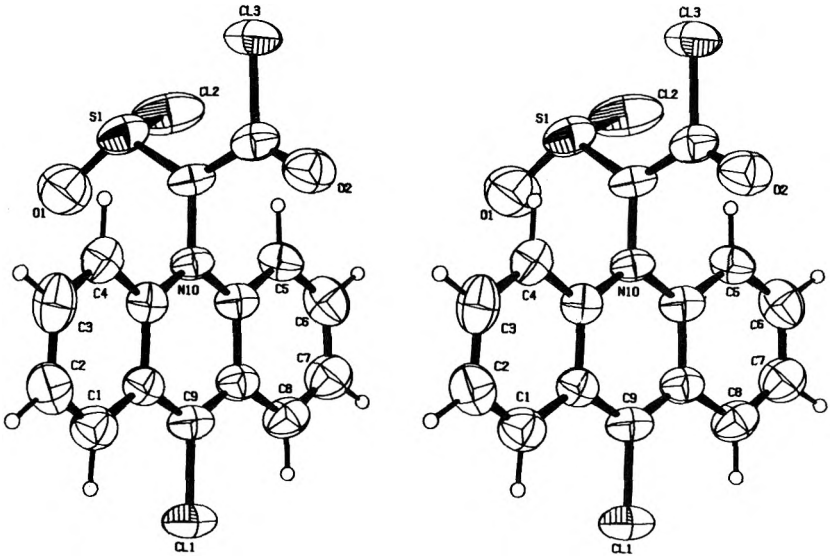
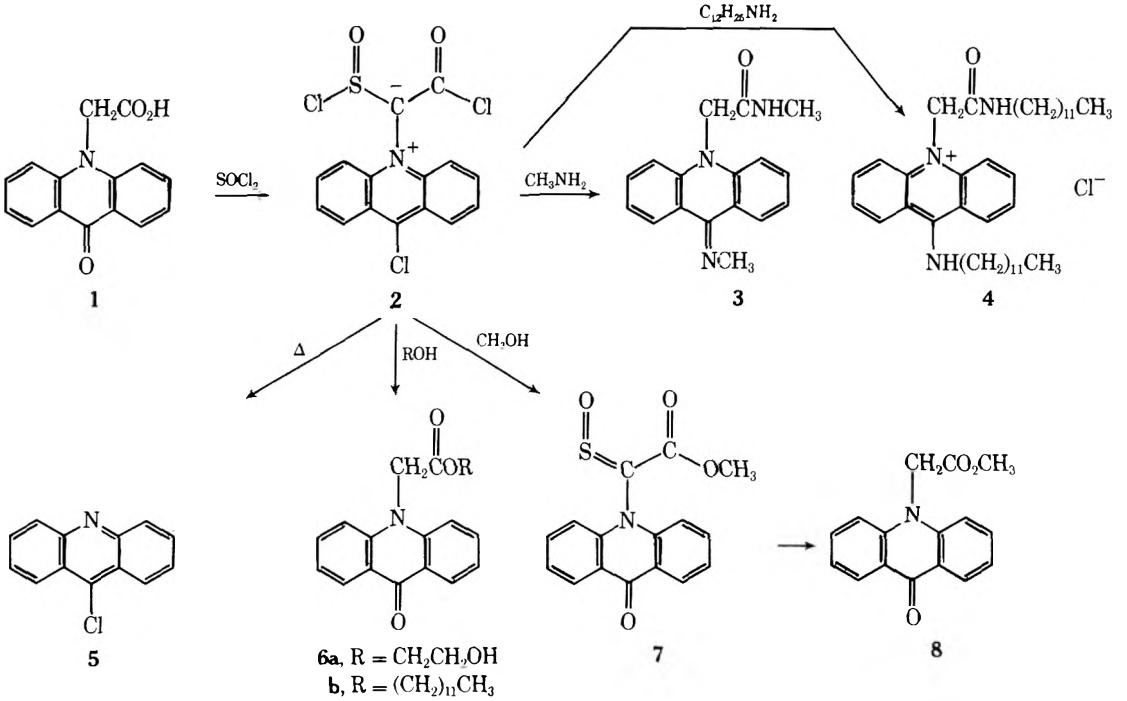


Figure 1. A stereoscopic drawing of a molecule of **2**. The thermal ellipsoids are scaled to the 50% probability level and the hydrogen atoms are shown as spheres of an arbitrary size.

of **2** (Figure 1) and some bond lengths and bond angles are also given. Apparently in addition to the formation of acid chloride function, thionyl chloride has reacted with 9-oxo-10-acridanacetic acid (**1**) at two additional sites as shown in structure **2**. The conversion of 10-alkyl-9-acridanone to 10-alkyl-9-chloroacridinium salts with thionyl chloride is known.[3] The sulfinylation of the methylene group is more interesting. Similar oxidizing reactions of thionyl chloride are known in the literature.[4] Although α-chlorosulfinyl species such as **2** have been proposed[4b,c] as initial intermediates in complex oxidative reaction sequences involving carboxylic acids and thionyl chloride, such sulfinyl chlorides have not been isolated in these reactions. The isolation is possible here probably owing to the crystallization of the stable ylide, in the absence of nucleophiles.

The carbon–sulfur bond in **2** was found to be very readily cleaved by protonic reagents. Thus on reaction with methylamine, dodecylamine, ethylene glycol, and dodecanol, followed by brief exposure of the reaction mixtures to water during isolation of the products, the chlorosulfinyl group of **2** is readily lost in forming amides and esters of the acridanacetic acids **3**, **4**, **6a**, and **6b**, respectively. Under mild methanolysis conditions, we were able to isolate the unstable methyl 9-oxo-α-sulfinyl-10-acridanacetate (**7**). The sulfinyl group in **7**, however, was readily cleaved by mild hydrolysis to afford **8**. Compound **7** appears to be a rare example of an α-carbonyl-substituted[5] thioamide *S*-oxide.[6,7] Owing to the instability of **7**, we have not investigated the stereochemistry of the substituents on the sulfur atom. The presence of strong bands at 1173 and 1085 cm^{-1} in the infrared spectrum of **7** is consistent with those ascribed to the C=S=O group in related structures.[8,9]

Concurrent with the above reactions in the side chain, substitution reactions with nucleophiles occur at position 9 of the acridinium ring. Thus when **2** was treated with an excess of methylamine, the imine **3** was formed in 50% yield. In the case of dodecylamine, the 9-dodecylaminoacridinium chloride derivative **4** was obtained in 65% yield. The reaction of **2** with alcohols followed by brief exposure to water containing triethylamine during the isolation procedure generated the



carbonyl groups in position 9 of the acridine ring in all cases. Pyrolysis of **2** led to the loss of the side chain resulting in the known[10] 9-chloroacridine **5.**

The structure of **2** was unambiguously established from a crystal structure analysis. The conformation of a molecule of **2** is shown in Figure 1. The coordination about the sulfur atom is tetrahedral [the distances and angles about S are S–Cl, 2.331 (6); S–C, 1.668 (8); S–O, 1.462 (8) Å; Cl–S–C, 105.2 (3); Cl–S–O, 102.8 (4); C–S–O, 107.2 (4)°]. The S–Cl distance is substantially greater than the usual S–Cl distance of 2.01 Å[11] and the S–C distance is slightly shorter than that for S=C distances (1.71 ± 0.01[11]). Similar S–Cl distances [2.323 (3) and 2.259 (3) Å] were found in bis(*p*-chlorophenyl) sulfide[12] where the sulfur coordination is trigonal bipyramidal. The dihedral angle between the plane of the S–C–COCl moiety and the mean plane of the three fused rings is 77°. The three fused rings are not coplanar. The dihedral angle between the planes of the two C_6 rings of the fused ring system is 7.6°.

Experimental Section

All melting points were taken in capillaries heated in oil baths, and are corrected. Infrared spectra were determined on a Digilab FTS14 or a Perkin-Elmer 621 spectrometer, mass spectra on a Varian MAT CH5 or a CEC-21-110 spectrometer, nuclear magnetic resonance spectra on a Jeolco C-60H, a Varian XL-100, or a Varian HA-100 spectrometer, using tetramethylsilane as internal standard, and ultraviolet spectra with a Cary 14M or 15 recording spectrometer. Solvents used were of reagent grade purity. Petroleum ether used boils at 30–60 °C. Unless otherwise specified, all solvents were evaporated on a Büchi Rotavapor evaporator under water-aspirator pressure using a water bath set at 30–80 °C.

9-Chloroacridinium 2-Chloro-1-(chlorosulfinyl)-2-oxoethylide (2). A mixture of 75.90 g (0.30 mol) of 9-oxo-10-acridanacetic acid (**1**), 350 ml of thionyl chloride, and 500 ml of 1,2-dimethoxyethane was heated to reflux for 2 h. On cooling the crimson red prisms of **2** were obtained. These were collected by filtration, washed with 1,2-dimethoxyethane followed by ether, and then dried in vacuo at 60 °C. They weighed 106.0 g (95%), mp 205–208 °C. These crystals were used for x-ray crystallographic analysis, spectral, and elemental analyses without recrystallization: ir (KBr) 1690 (s), 1603 (m), 1570 (m), 1530 (m), 1378 (m), 1335 (m), 1270 (m), 1122 (s), 937 (s), and 763 cm^{-1} (s); uv max (CH_3CN) 208 nm (ϵ 20 200), 260 (39 500), 350 (sh, 6800), 365 (10 600), 388 (7850), and 430–480 (sh, 2100).

Anal. Calcd for $C_{15}H_8Cl_3NO_2S$: C, 48.35; H, 2.16; N, 3.76; Cl, 28.54; S, 8.60. Found: C, 48.60; H, 2.23; N, 3.65; Cl, 28.28; S, 8.78.

***N*-Methyl-9-(methylimino)-10-acridanacetamide (3).** A mixture of 7.40 g (20.0 mmol) of **2** and 0.380 mol of methylamine (100 ml of a 3.8 M solution in tetrahydrofuran) was stirred at room temperature for 1 h. To this was added 30 ml of water, and the mixture was evaporated. The residual oil was extracted into dichloromethane. The dichloromethane layer was dried (Na_2SO_4) and evaporated to dryness. The residue, on trituration with ether, afforded crude yellow amorphous solid which was recrystallized from ethanol to give 2.70 g (50%) of **3** as tan prisms: mp 234–236 °C; ir (KBr) 3280, 1660, 1626, and 1600 cm^{-1}; uv max (ethanol) 220 nm (ϵ 28 200), 245 (sh, 22 300), 257 (25 300), 268 (24 800) 285 (sh, 9700), 377 (7300), 410 (4200), and 430 (4000); NMR ($CDCl_3$) δ 2.75 (d, 3, $NHCH_3$), 3.69 (s, 3, NCH_3), and 4.58 ppm (s, 2, CH_2); mass spectrum *m/e* 279 (M^+).

Anal. Calcd for $C_{17}H_{17}N_3O$: C, 73.10; H, 6.13; N, 15.04. Found: C, 72.90; H, 6.13; N, 15.27.

9-(Dodecylamino)-10-[(dodecylcarbamoyl)methyl]acridinium Chloride (4). A mixture of 15.0 g (42.0 mmol) of **2**, 25.0 g (135 mmol) of dodecylamine, and 500 ml of tetrahydrofuran was stirred at room temperature for 2 h. After the addition of 50 ml of water, tetrahydrofuran was evaporated. The residual aqueous suspension was extracted with dichloromethane. The dichloromethane layer was dried (Na_2SO_4) and evaporated to dryness. The residue on trituation with ether afforded a solid which was recrystallized from methanol yielding 15.20 g (65%) of **4** as yellow needles: mp 174–176 °C; ir (KBr) 3200, 1685, and 1590 cm^{-1}; uv max (2-PrOH) 222 nm (ϵ 22 000), 260 (sh, 35 600), 271 (49 000), 290 (sh, 7000), 322 (sh, 2300), 417 (10 800), and 437 (10 600); mass spectrum *m/e* 587 (M^+ of free base).

Anal. Calcd for $C_{39}H_{62}ClN_3O$: C, 75.02; H. 10.00; N, 6.73; Cl, 5.68. Found: C, 74.86; H, 9.90; N, 6.62; Cl, 5.74.

9-Chloroacridine (5).[10] A mixture of 5.00 g (13.40 mmol) of **2** and 25 ml of mineral oil was heated to 210 °C till all gaseous evolution had ceased (0.5 h). On cooling, filtration and washing with petroleum ether afforded 3.0 g of 9-chloroacridinium chloride as a greenish-yellow solid, mp 244–247 °C. This material was sublimed at 180–200 °C in vacuo to afford 1.60 g of yellow-red prisms, mp 248–250 °C. An analytical sample was prepared by recrystallization from acetonitrile to afford yellow needles, mp 245–248 °C.

Anal. Calcd for $C_{13}H_9Cl_2N$: C, 61.10; H, 3.55; N, 5.48. Found: C, 61.43; H, 3.69; N, 5.56.

A mixture of 250 mg (1.0 mmol) of 9-chloroacridinium chloride, 10 ml of 2 N sodium hydroxide, and 10 ml of dichloromethane was stirred at room temperature for 5 min. The dichloromethane layer was dried (Na_2SO_4) and evaporated to dryness. The residue on crystallization from dichloromethane–petroleum ether afforded 110 mg of **5** as buff prisms, mp 118–120 °C (lit.[10] mp 119–120 °C).

2-Hydroxyethyl 9-Oxo-10-acridanacetate (6a). A mixture of 10.0 g (27.0 mmol) of **2** and 35 ml of ethylene glycol was stirred at room temperature for 16 h. This reaction mixture was poured into a mixture of 25 ml of triethylamine, 500 ml of dichloromethane, and 500 ml of water. The dichloromethane layer was dried (Na_2SO_4) and evaporated to dryness. The residue on crystallization from acetone–hexane afforded 3.50 g (45%) of **6a** as light cream needles, mp 169–172 °C. Recrystallization from acetone–hexane afforded cream needles: mp 175–178 °C; ir (KBr) 3430, 1730, 1630, and 1600 cm^{-1}; uv max (2-PrOH) 214 nm (ϵ 26 400), 253 (52 400), 290 (2600), 355 (sh, 3900), 374 (9000), and 394 (11 000); NMR ($CDCl_3$) δ 5.20 (s, 2, NCH_2); mass spectrum *m/e* 297 (M^+).

Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.67; H, 5.08; N, 4.71. Found: C, 68.53; H, 5.05; N, 4.61.

Dodecyl 9-Oxo-10-acridanacetate (6b). A mixture of 10.0 g (27.0 mmol) of **2** and 35 ml of dodecanol was stirred at room temperature for 16 h. This mixture was then poured into a mixture of 25 ml of triethylamine, 500 ml of dichloromethane, and 500 ml of water. The dichloromethane layer was dried (Na_2SO_4) and evaporated to dryness. The residue on crystallization from petroleum ether afforded 8.50 g (75%) of **6b** as buff needles, mp 74–77 °C. Recrystallization from dichloromethane–petroleum ether afforded buff needles: mp 79–81 °C; ir (KBr) 1730, 1630, and 1600 cm^{-1}; uv max (2-PrOH) 214 nm (ϵ 22 650), 253 (49 950), 299 (2550), 358 (sh, 4400), 376 (8700), and 394 (10 500); NMR ($CDCl_3$) δ 5.04 (s, 2, NCH_2); mass spectrum *m/e* 421 (M^+).

Anal. Calcd for $C_{27}H_{35}NO_3$: C, 76.92; H, 8.36; N, 3.32. Found: C, 77.21; H, 8.35; N, 3.34.

Methyl 9-Oxo-α-sulfinyl-10-acridanacetate (7). A mixture of 37.20 g (10.0 mmol) of **2** and 500 ml of methanol was stirred at room temperature for 2 h. A clear red solution formed. On additional stirring, **7** precipitated as a pink, amorphous solid. This was collected by filtration, washed with methanol, and dried at 60 °C. It weighed 20.0 g (65%), mp 176–178 °C. On recrystallization from dichloromethane–petroleum ether, red prisms were obtained: mp 173–175 °C; ir (KBr) 1740, 1638, 1606, 1173, and 1085 cm^{-1}; uv max (2-PrOH) 214 nm (ϵ 20 900), 252 (42 400), 285 (sh, 6500), 365 (sh, 6500), 378 (7200), 395 (sh, 3100), and 455 (490); NMR showed no CH_2 signal; mass spectrum *m/e* 313 (M^+).

Anal. Calcd for $C_{16}H_{11}NO_4S$: C, 61.33; H, 3.53; N, 4.47; S, 10.23. Found: C, 61.55; H, 3.57; N, 4.57; S, 10.09.

Methyl 9-Oxo-10-acridanacetate (8). A mixture of 10.0 g (32.0 mmol) of **7**, 10 ml (71.0 mmol) of triethylamine, 300 ml of dichloromethane, and 300 ml of water was stirred at room temperature for 0.5 h. The dichloromethane layer was separated, dried (Na_2SO_4), and evaporated to dryness. The residue on crystallization from dichloromethane–petroleum ether afforded 4.70 g (55%) of **8** as colorless needles, mp 207–209 °C. The melting point was unchanged on recrystallization from the same solvents: ir (KBr) 1740, 1630, and 1600 cm^{-1}; uv spectrum (2-PrOH) essentially the same as those of **6a** and **6b**; NMR ($CDCl_3$) δ 5.05 (s, 2, NCH_2); mass spectrum *m/e* 267 (M^+).

Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.71; H, 4.88; N, 5.14.

Crystallography. Crystals of **2** ($C_{15}H_8Cl_3NO_2S$, mol wt 372.66) are monoclinic, space group $P2_1/c$, with a = 8.620 (9), b = 11.942 (18), c = 14.958 (12) Å, β = 103.03 (5)°, and d_{calcd} = 1.649 g cm^{-3} for Z = 4.

The intensity data were measured on a Hilger-Watts diffractometer (Ni filtered Cu Kα radiation, θ–2θ scans, pulse height discrimination). The size of the crystal used for data collection was approximately 0.08 × 0.2 × 0.5 mm. A total of 2400 independent reflections (θ <57°) were measured, of which 1409 had intensities which were significantly greater than background [$I > 2.5\sigma(I)$]. The data were corrected for absorption (μ = 68.3 cm^{-1}). The structure was solved by a multiple solution procedure[13] and was refined by full-matrix least squares. The

positions of the hydrogen atoms were calculated after preliminary refinement of the structure. In the final refinement anisotropic thermal parameters were used for the heavier atoms and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations but their parameters were not refined. The final discrepancy index is $R = 0.069$ for the 1409 observed reflections. A difference map has no peaks greater than ± 0.2 eÅ^{-3}.

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Registry No.—**1**, 38609-97-1; **2**, 59922-55-3; **3**, 59922-56-4; **4**, 59922-57-5; **5**, 1207-69-8; **6a**, 59922-58-6; **6b**, 59922-59-7; **7**, 59922-60-0; **8**, 59922-61-1; thionyl chloride, 7719-09-7; methylamine, 74-89-5; dodecylamine, 124-22-1; 9-chloroacridinium chloride, 19255-74-4; ethylene glycol, 107-21-1; dodecanol, 112-53-8.

Supplementary Material Available. Tables of the positional and thermal parameters for the structure of **2** (2 pages). Ordering information is given on any current masthead page.

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N-Arenesulfonyl Isocyanurates

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Several new synthetic methods are described for the preparation of *N*-mono- and bis(arenesulfonyl) substituted hexahydro-*s*-triazine-2,4,6-triones (isocyanurates). Base-catalyzed cycloaddition reactions of arenesulfonyl isocyanates and alkyl (aryl) isocyanates give exclusively 1-alkyl- (aryl-) 3,5-bis(arenesulfonyl) isocyanurates (**1**). Degradation of 1,3-dimethyl-5-phenyl-6,6-bis(dimethylamino)hexahydro-*s*-triazine-2,4-dione (**7**) with arenesulfonyl isocyanates leads to 1-methyl-3-phenyl-5-arenesulfonyl isocyanurates (**10**). Differently substituted **10** can also be synthesized from *N*-methyl-*N'*-arenesulfonylureas and aryl isocyanates in presence of base. Heating of arenesulfonamides and aryl isocyanates in presence of catalytic amounts of triethylamine yields 1,3-diaryl-5-arenesulfonyl isocyanurates (**11**).

Trisubstituted isocyanurates are readily obtained by base-catalyzed trimerization of alkyl and aryl isocyanates.[1] This reaction cannot be extended to arenesulfonyl isocyanates, because the initially formed dipolar 1:1 adducts with organic or inorganic bases do not undergo further reactions with excess sulfonyl isocyanates. Mixed oligomerizations of aryl or alkyl isocyanates with sulfonyl isocyanates leading to partially N-sulfonylated isocyanurates are also not known. Recently, 1-arenesulfonyl-3,5-dialkyl isocyanurates were obtained from the reaction of arenesulfonamides with alkyl isocyanates in the presence of triethylamine.[2,3] We now wish to report several routes for the convenient synthesis of N-persubstituted isocyanurates with one or two *N*-arenesulfonyl groups.

A. 1-Alkyl- (aryl-) 3,5-bis(arenesulfonyl)hexahydro-*s*-triazine-2,4,6-triones. In our investigations related to the selective stepwise oligomerization of isocyanates we studied the feasibility of base-catalyzed cotrimerizations of aryl as well as alkyl isocyanates with arenesulfonyl isocyanates. It is conceivable that the initially formed 1:1 adduct derived from arenesulfonyl isocyanate and certain heterocyclic tertiary amines would undergo reaction with alkyl or aryl isocyanates to yield 1,3-dialkyl- (aryl-) 5-arenesulfonyl or (and) 1-alkyl- (aryl-) 3,5-bis(arenesulfonyl) isocyanurates. Mixtures of alkyl or aryl isocyanates and arenesulfonyl isocyanates in molar ratios of 1:1 or 2:1 containing catalytic amounts of 1,2-dimethylimidazole (10–15 mol %)[4] solidify on standing at room temperature for a prolonged period of time (from 72 to 144 h). On workup of the crystalline reaction products with methanol, 1-alkyl- (aryl-) 3,5-bis(arenesulfonyl)hexahydro-*s*-triazine-2,4,6-triones **1a–e** are left behind undissolved in moderate to good yields (see Table I). The formation of the cotrimers **1**, derived from 2 mol of sulfonyl and 1 mol of alkyl or aryl isocyanate, seems to be independent of the molar ratio of the reactants since excess alkyl or aryl isocyanate did not alter the molar composition of the products.

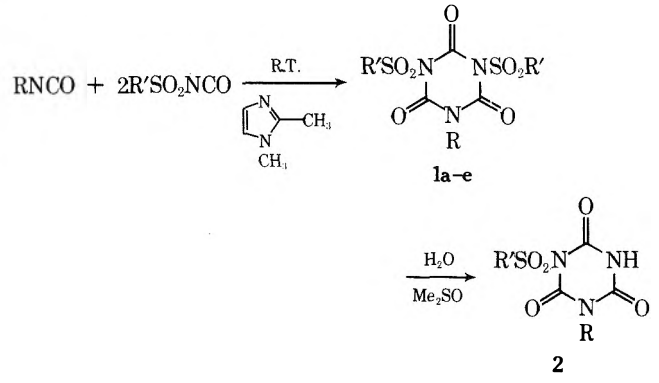
The isocyanurates of type **1** can be readily purified by reprecipitation from acetone–water. Attempted recrystallization of **1c** from dimethyl sulfoxide (Me_2SO)–water, however, leads to the hydrolytic removal of one of the *p*-toluenesulfonyl groups, giving 1-phenyl-3-(*p*-toluenesulfonyl)hexahydro-*s*-triazine-2,4,6-trione (**2**). The hydrolysis is best conducted by briefly heating a solution of **1c** in Me_2SO–water (volume ratio of 4:1) to 130 °C. The reaction can also be followed by monitoring the changes of the ^1H NMR spectrum of **1c** in wet Me_2SO-d_6 over a period of 60 min (at room temperature). The spectrum shows initially a singlet for the two protons of the two CH_3 groups of the *p*-tolyl moieties at δ 2.35 ppm. Slow disappearance of this signal and simultaneous appearance of

Table I. *N*-Sulfonyl Isocyanurates[a]

Compd	R	R′	Mp, °C	Yield, %	Reaction duration, h	Ir (C=O), cm^{-1} in $CHCl_3$, KBr[b]
1a	CH_3	*p*-ClC_6H_4	238	69	96	1720, 1700 (1740, 1715)
1b	CH_3	*p*-$CH_3C_6H_4$	217–218	40	96	1735, 1715 (1745, 1730, 1715)
1c	C_6H_5	*p*-$CH_3C_6H_4$	245	57	72	1740, 1720 (1735, 1715)
				75	144	
1d	C_6H_5	*p*-ClC_6H_4	241–243 dec	58	96	1735, 1725 (sh) (1735 broad)
1e	*p*-$CH_3C_6H_4$	*p*-ClC_6H_4	228–230	73	72	1740, 1730 (sh) (1740 broad)
1f	*m*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	238–239	80	3 months	1740, 1720
2	C_6H_5	*p*-$CH_3C_6H_4$	205	86		(1730 [sh], 1710)
10a	*p*-$CH_3C_6H_4$	C_6H_5	265–266	62[c]		1710 (1720, 1705)
				41[d]	120	
10b	*p*-ClC_6H_4	C_6H_5	260–265	86		1710 (1705, 1685)
10c	*p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	235–237	38[e]	120	1715
11a	C_6H_5	C_6H_5	305	42	96	1730 (sh), 1720, 1700 (sh) (1730, 1710)
11b	*m*-$CH_3C_6H_4$	C_6H_5	284–285	35	96	1730 (sh), 1720, 1700 (sh) (1730 [sh], 1710)
11c	C_6H_5	*p*-$CH_3C_6H_4$	>300	49	96	1730 (sh), 1715, 1700 (sh) (1730 [sh], 1725, 1710)
11d	*m*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	288	27	64	1725 (sh), 1710, 1695 (sh) (1730 [sh], 1710)
11e	$C_6H_5CH_2$	*p*-$CH_3C_6H_4$	246–247	17[f]	120	1715, 1700
11f	*p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	288	28[g]	140	1720 (broad)

[a] Satisfactory analytical values (±0.3% for C, H, N) were reported for all compounds. Ed. [b] Values in parentheses in KBr. [c] From compound 7 and *p*-toluenesulfonyl isocyanate. [d] From *N*-methyl-*N*′-(*p*-toluenesulfonyl)urea and phenyl isocyanate. [e] From *N*-methyl-*N*′-(*p*-toluenesulfonyl)urea and *p*-tolyl isocyanate. [f] From *N*-phenyl-*N*′-(*p*-toluenesulfonyl)urea and benzyl isocyanate. [g] From *N*-phenyl-*N*′-(*p*-toluenesulfonyl)urea and *p*-tolyl isocyanate.

a new singlet at δ 2.30 ppm, indicating the transformation **1c** → **2**, can be observed within minutes. Since no other CH_3 signal is visible in the spectrum the methyl group of the by-product, *p*-toluenesulfonic acid, must be hidden underneath the new signal. A similar hydrolytic removal of a *N*-arenesulfonyl group has been reported for 1-(*p*-iodobenzenesulfonyl)-3,5-di-*n*-propyl isocyanurate.[2]

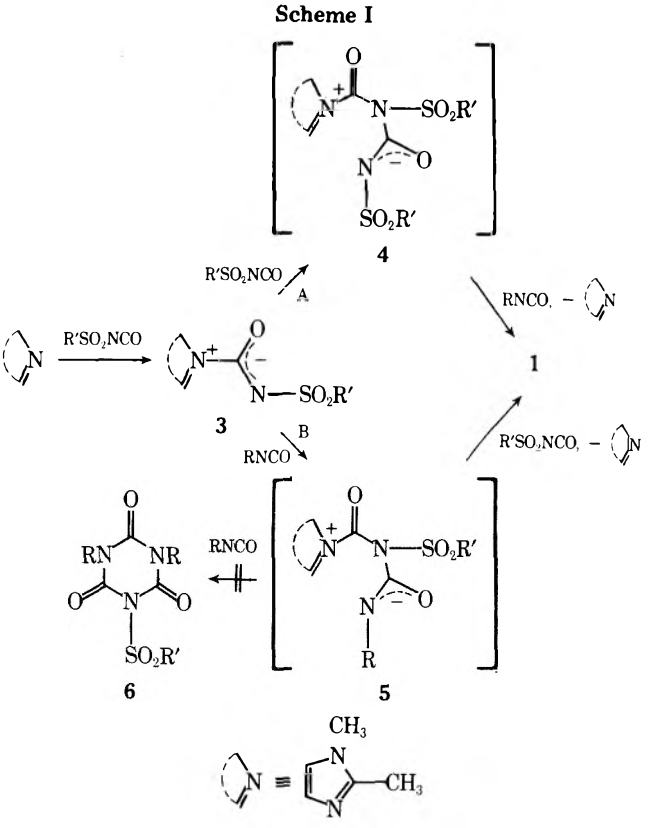


It is assumed that the cotrimers **1a–e** are products derived via a sequence of reactions involving dipolar intermediates (Scheme I). Initially a dipolar sulfonyl isocyanate–catalyst adduct **3** is formed, which can be intercepted either by a second molecule of sulfonyl isocyanate to give **4** or by alkyl (aryl) isocyanate, giving **5**. Further reaction of these dipoles with more isocyanate—sulfonyl or alkyl (aryl)—as indicated followed by expulsion of the catalyst produces the cotrimers **1**.

That adducts of type **3** are formed as initial products could be verified by independent experiments. Mixing equimolar quantities of *p*-toluenesulfonyl isocyanate and 1,2-dimethylimidazole in acetone produces instantaneously **3** (R′ = *p*-$CH_3C_6H_4$) in 93% yield. Changing the molar ratio from 1:1 to 2:1 with sulfonyl isocyanate in excess or adding 1 mol of phenyl isocyanate to the mixture does not interfere with the initial formation of **3**. Similar adducts are known to be formed from other nitrogen bases and sulfonyl isocyanates.[5,6]

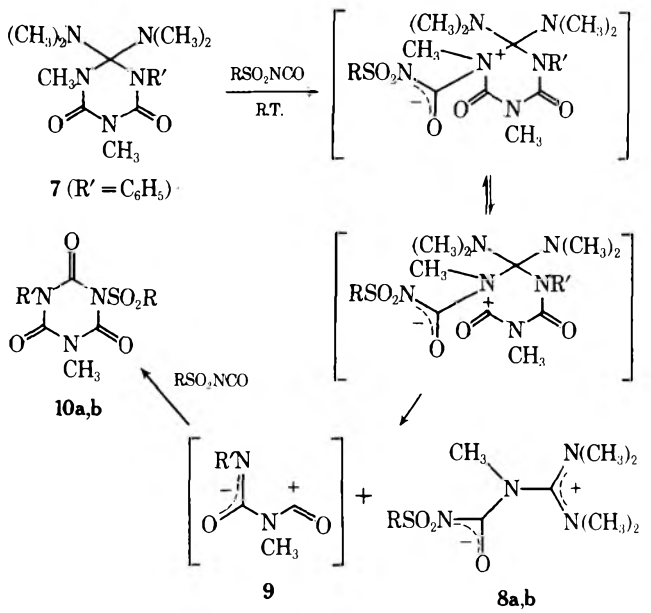
Attempts to oligomerize *p*-toluenesulfonyl isocyanate alone leading to either the unknown dimer or trimer failed. No

Scheme I



changes could be observed in the ir spectra of a sample of the isocyanate containing only catalytic amounts of 1,2-dimethylimidazole, which was kept for 30 days at room temperature. This observation could indicate that the 1:1 adducts **3** are not intercepted by excess arenesulfonyl isocyanate (which would lead to **4**) but rather by aryl isocyanate, giving **5**. In the next step, leading to **1**, however, the preference of the dienophile attack at the dipole **5** is again reversed since no isocyanurates **6**, derived from 2 mol of alkyl (aryl) isocyanate and 1 mol of sulfonyl isocyanate, are obtained in these reactions. The exclusive formation of type **1** isocyanurates was also

Scheme II



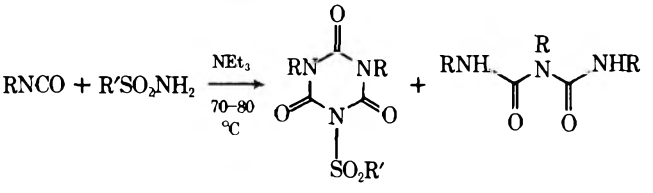
demonstrated in an experiment in which an equimolar mixture of *p*-toluenesulfonyl and *m*-tolyl isocyanate and catalytic amounts of 1,2-dimethylimidazole was kept for 3 months at room temperature. Workup with methanol gave an 80% crude yield of **1f** but no corresponding **6** (R = *m*-$CH_3C_6H_4$).[7] Analytical data and yields of all the new isocyanurates **1a–f** are listed in Table I.

B. 1-Alkyl-3-aryl-5-(arenesulfonyl)hexahydro-*s*-triazine-2,4,6-triones. Isocyanurates, derived from 1 mol of alkyl, aryl, and arenesulfonyl isocyanate, each can be prepared by treating a solution of 1,3-dimethyl-5-phenyl-6,6-bis(dimethylamino)hexahydro-*s*-triazine-2,4-dione (**7**)[8] with 2 mol of arenesulfonyl isocyanate at room temperature. The new isocyanurates **10** precipitate within minutes from the reaction mixtures in good yield. Dipolar adducts of type **8**[6] composed of 1 mol of pentamethylguanidine and arenesulfonyl isocyanate are obtained as side products (**8a** with R = *p*-$CH_3C_6H_4SO_2$ could be isolated in 52% yield in the reaction of **7** with *p*-toluenesulfonyl isocyanate). We also attempted to synthesize the cotrimers **10** by mixing the three parent isocyanates, i.e., methyl, phenyl, and *p*-toluenesulfonyl isocyanate but did not observe any reaction (as followed by ir) even after standing for 24 h. Addition of small amounts of pentamethylguanidine to the mixture did not catalyze the oligomerization, thus eliminating the possible formation of **8** and **10** from dissociation products of **7** (methyl and phenyl isocyanate).

It is more likely that the formation of **8** and **10** from **7**, which involves degradation and re-formation of a *s*-triazine ring, proceeds via cleavage of the C–N bond at positions 2–3 after attack of arenesulfonyl isocyanate. Further possible reaction steps are outlined in Scheme II.

This reaction is related to similar displacements of one dipolarophile by another in cycloadducts derived from isocyanates and isoquinoline as described by Huisgen and coworkers.[9]

C. 1,3-Diaryl-5-(arenesulfonyl)hexahydro-*s*-triazine-2,4,6-triones. In extending the reported synthesis of N-sulfonylated isocyanurates from arenesulfonamides and alkyl isocyanates in the presence of triethylamine[2,3] to aryl isocyanates we were able to obtain 1,3-diaryl-5-arenesulfonylhexahydro-*s*-triazine-2,4,6-triones **11a–d** in moderate yield

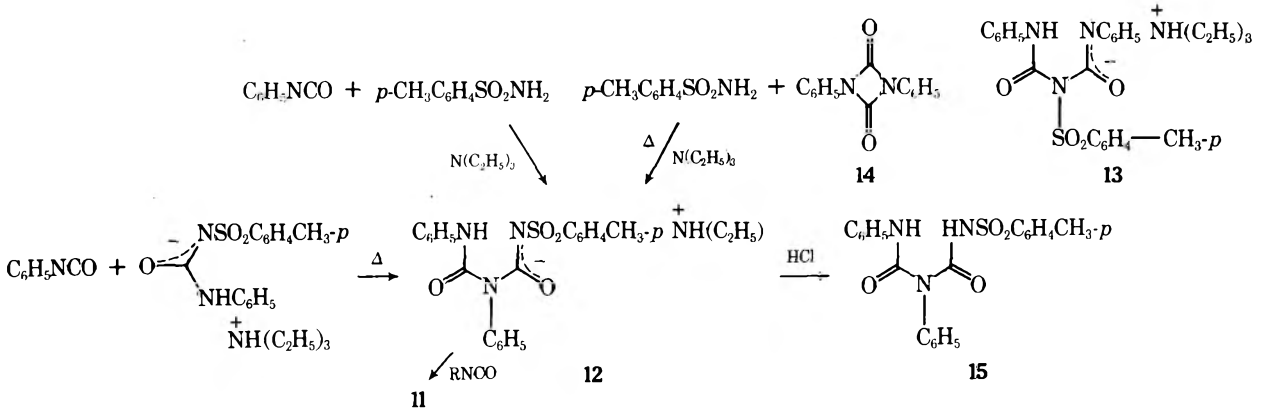


(see Table I for yields). By-products in these reactions, which are carried out by heating sulfonamides with excess aryl isocyanate and catalytic amounts of triethylamine for 64–96 h to 70–80 °C, are *N,N′,N″*-triarylbiurets.

When a mixture of equimolar amounts of *p*-toluenesulfonamide and triethylamine in excess phenyl isocyanate is kept at room temperature for several hours, a precursor of the expected isocyanurates with a molar composition of 1:2:1 (*p*-toluenesulfonamide:phenyl isocyanate:triethylamine) is obtained in nearly quantitative yield. This intermediate was found to be the triethylammonium salt of *N,N′*-diphenyl-*N″*-(*p*-toluenesulfonyl)biuret **12**. Compound **12** can also be prepared in 43% yield on heating a chloroform solution of equimolar amounts of 1,3-diphenyldiazetidine-2,4-dione **14**, *p*-toluenesulfonamide, and triethylamine for 23 h. A mixture of **14** and *p*-toluenesulfonamide heated in the absence of triethylamine in chloroform remains unchanged while carbanilide and *N,N*-dimethyl-*N′*-(*p*-toluenesulfonyl)formamidine are obtained in dimethylformamide at 120 °C. The biuret salt **12** is also produced in 54% yield on heating the triethylammonium salt of *N*-phenyl-*N′*-(*p*-toluenesulfonyl)urea with equimolar amounts of phenyl isocyanate for 4 h in chloroform (see Scheme III).

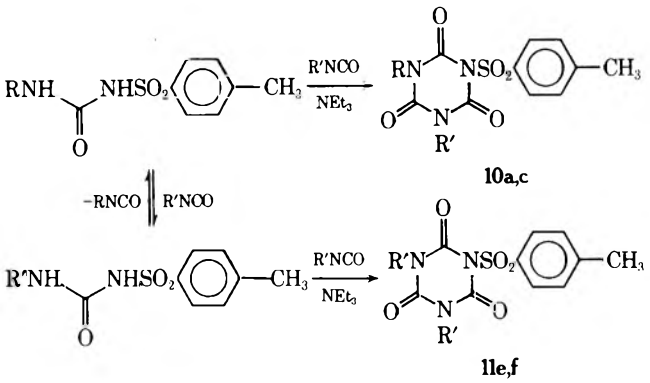
The free *N,N′*-diphenyl-*N″*-(*p*-toluenesulfonyl)biuret **15** is formed in 90% yield on treating a methylene chloride solution of **12** with hydrogen chloride. The proposed asymmetric structure of the biuret **15** and its salt **12** was confirmed by ^{13}C NMR spectroscopy. A spectrum of **15** in $CDCl_3$ showed two distinctly different carbonyl carbons at δ 153.3 and 150.4 ppm, thus eliminating the symmetric formula **13** for the reaction product.

Scheme III



The biuret **15** can readily be converted in 52% yield into **11c** on heating with excess phenyl isocyanate and a catalytic amount of triethylamine at 75 °C for 96 h. Using the triethylammonium salt **12** in a similar reaction led to about 10% **11c** after 15 h reaction duration while most of the excess phenyl isocyanate was trimerized under the influence of triethylamine.

The stepwise formation of isocyanurates of type **11** via *N*-arenesulfonylureas and biurets allows also the synthesis of isocyanurates with three different substituents. If *N*-methyl-*N'*-(*p*-toluenesulfonyl)urea is heated with excess phenyl isocyanate and catalytic amounts of triethylamine to 80 °C for 120 h, 1-methyl-3-phenyl-5-(*p*-toluenesulfonyl)-isocyanurate (**10a**) is obtained in 41% yield. Similarly, **10c** is obtained on heating the same urea with *p*-tolyl isocyanate (38% yield). On heating *N*-phenyl-*N'*-(*p*-toluenesulfonyl)urea with excess of either benzyl or *p*-tolyl isocyanate and triethylamine, however, not the expected **10d** and **10e** but rather **11e** and **11f** were obtained in low yields (17 and 23%, respectively).



Their formation can readily be explained by an exchange of substituents in the urea during heating with excess benzyl or *p*-tolyl isocyanate.

Experimental Section[10]

General Procedure for the Preparation of 1-Alkyl- (aryl-) 3,5-bis(arenesulfonyl)hexahydro-*s*-triazine-2,4,6-triones 1a–f. On adding 0.02 mol of 1,2-dimethylimidazole to a mixture of 0.16 mol of alkyl (or aryl) isocyanate and 0.16 mol of arenesulfonyl isocyanate, a colorless precipitate was formed instantaneously which was redissolved on gentle heating of the suspension. The reaction mixtures solidified on standing at room temperature for prolonged periods of time. The resulting crystal cake was taken up in ca. 70 ml of methanol and filtered, and the residue was washed with methanol and finally with diethyl ether leaving the isocyanurates as colorless crystals. Samples were recrystallized for analysis from acetone–water or acetone–methanol; the spectral data are given in Table I.

1-Phenyl-3-(*p*-toluenesulfonyl)hexahydro-*s*-triazine-2,4,6-trione (2). A suspension of 2.0 g (0.0039 mol) of **1e** in 4 ml of dimethyl sulfoxide and 1 ml of water was placed into a preheated oil bath at 130 °C. A clear solution was formed almost immediately from which colorless crystals precipitated within a few minutes. The reaction was stopped after 5 min, the mixture cooled and filtered, and the residue washed with water, leaving 1.2 g (86%) of **2**, mp (from acetone–water) 205 °C.

1,2-Dimethyl-3-(*p*-toluenesulfocarbamoyl)imidazolium Inner Salt 3 (R' = *p*-$CH_3C_6H_4$). On mixing 0.96 g (0.01 mol) of 1,2-dimethylimidazole and 2.00 g (0.01 mol) of *p*-toluenesulfonyl isocyanate in ca. 25 ml of acetone, colorless crystals were precipitated at once while the mixture became warm. After standing for 30 min, the precipitate was collected and washed with acetone and finally diethyl ether; 2.75 g (93%) of **3** was obtained as colorless plates, mp 155 °C dec.

Anal. Calcd for $C_{13}H_{15}N_3O_3S$: C, 53.24; H, 5.16; N, 14.33. Found: C, 53.01; H, 5.24; N, 14.18.

The dipolar adduct can also be obtained from similar reaction mixtures containing either larger amounts of *p*-toluenesulfonyl isocyanate (0.02 mol, 90% yield of **3**) or 0.01 mol of phenyl isocyanate (88% yield of **3**).

1-Methyl-3-phenyl-5-(*p*-toluenesulfonyl)hexahydro-*s*-triazine-2,4,6-trione (10a). A. From 1,3-Dimethyl-5-phenyl-6,6-bis(dimethylamino)hexahydro-*s*-triazine-2,4-dione (7) and *p*-Toluenesulfonyl Isocyanate. An exothermic reaction took place on gradually adding 3.90 g (0.02 mol) of *p*-toluenesulfonyl isocyanate to a solution of 3.05 g (0.01 mol) of 1,3-dimethyl-5-phenyl-6,6-bis(dimethylamino)hexahydro-s-triazine-2,4-dione (**7**)[8] in 25 ml of chloroform. Colorless crystals of **10a** precipitated on cooling the solution to −5 °C for 18 h; filtration yielded 2.3 g (62%) of **10a**, recrystallized for analysis from acetone–water. Colorless crystals of **8a** (R = *p*-$CH_3C_6H_4$) were deposited on diluting the chloroform filtrate with diethyl ether: 1.7 g (52%); mp 210–217 °C dec (from methylene chloride–diethyl ether); ir ($CHCl_3$) 1650, 1605 cm^{-1} (C=N and C=O bands).

Anal. Calcd for $C_{14}H_{22}N_4O_3S$: C, 51.52; H, 6.80; N, 17.17; S, 9.82. Found: C, 51.54; H, 6.75; N, 17.24; S, 9.84.

The isocyanurate **10b** was prepared similarly. In this case the corresponding **8b** was not isolated from the reaction mixture.

B. From *N*-Methyl-*N'*-(*p*-toluenesulfonyl)urea and Phenyl Isocyanate. A mixture of 9.12 g (0.04 mol) of *N*-methyl-*N'*-(*p*-toluenesulfonyl)urea, 24.0 g (0.2 mol) of phenyl isocyanate, and 1.0 g (0.01 mol) of triethylamine was heated under exclusion of air to 80 °C for 120 h. Crystals started to separate from the initially clear reaction solution. Unreacted isocyanate was removed under vacuum, and the crystalline residue was triturated with methanol. Filtration gave a mixture of **10a** and *N,N',N''*-triphenylbiuret (15.0 g). The crude mixture was dissolved in hot chloroform and on dilution with methanol, 6.1 g (41%) of **10a** precipitated in the form of colorless crystals, identical in mixture melting point and ir with **10a** obtained under A. On concentrating the filtrate, 4.0 g of *N,N',N''*-triphenylbiuret can be isolated. Isocyanurate **10c** (R = R' = *p*-$CH_3C_6H_4$) was prepared similarly using *p*-tolyl isocyanate; yields are given in Table I.

General Procedure for the Preparation of 1,3-Diaryl-5-(arenesulfonyl)hexahydro-*s*-triazine-2,4,6-triones 11a-d. Mixtures consisting of 0.2 mol of aryl isocyanate, 0.04 mol of arenesulfonamide, and 0.01 mol of triethylamine were heated to 70–80 °C for a prolonged period of time, resulting in the nearly complete solidification of the flask content. The crude products were treated with methanol and filtered, leaving mixtures of the isocyanurate **11** and the corresponding *N,N',N''*-triarylbiuret. Satisfactory separation of the two components was possible by dissolving the crude products in hot chloroform and treating the solutions with approximately double the volume of methanol, causing a nearly quantitative precipitation of the isocyanurate, very often analytically pure, while the biurets remained dissolved. The crude isocyanurates can be recrystallized from acetone–water or chloroform–methanol. The biurets crystallized on concentrating the filtrates and were purified by recrystallization from methanol.

Isocyanurate 11c from *N,N'*-Diphenyl-*N''*-(*p*-toluenesulfonyl)biuret 15 and Phenyl Isocyanate. A mixture of 1.0 g (0.0025 mol) of **15**, 2.0 g (0.017 mol) of phenyl isocyanate, and 0.1 g of triethylamine was heated for 96 h to 75 °C. The partially solidified reaction product was triturated with methanol, and the undissolved colorless crystals were filtered off and washed with methanol. The crude product, 1.0 g of a mixture of **11c** and some *N,N',N''*-triphenylbiuret (ir), was treated with boiling methanol, leaving 0.55 g (52%) of pure **11c** undissolved. The material was identical in ir comparison with **11c** prepared according to the above procedure. Concentration of the filtrate yielded *N,N',N''*-triphenylbiuret.

Isocyanurates 11e and 11f from *N*-Phenyl-*N'*-(*p*-toluenesulfonyl)urea and Benzyl or *p*-Tolyl Isocyanate. Colorless precipitates were formed on heating a mixture of 0.02 mol of *N*-phenyl-*N'*-(*p*-toluenesulfonyl)urea and 0.1 mol of benzyl or *p*-tolyl isocyanate for 120 h to 80 °C. After most of the excess isocyanates were removed by vacuum distillation the residues were triturated with methanol, and the crude mixtures of isocyanurate and the corresponding N,N',N''-trisubstituted biuret were dissolved in hot chloroform. The isocyanurates can be precipitated from the solutions by adding methanol; yields are in Table I. On concentration of the filtrates the corresponding trisubstituted biurets can be isolated.

***N,N'*-Diphenyl-*N''*-(*p*-toluenesulfonyl)biuret 15 and Its Triethylammonium Salt 12. A. From Phenyl Isocyanate and *p*-Toluenesulfonamide.** A mixture of 3.40 g (0.02 mol) of *p*-toluenesulfonamide, 12.0 g (0.1 mol) of phenyl isocyanate, and 2.0 g (0.02 mol) of triethylamine was kept at room temperature for 18 h. The initially clear reaction mixture became warm, and colorless crystals separated on standing. The formed suspension was diluted with diethyl ether, and the crystals were filtered off and washed with ether, leaving 4 g (92%) of **12**, mp 129–131 °C dec (from $CHCl_3$–diethyl ether); ir ($CHCl_3$) 1680 cm^{-1} (C=O).

Anal. Calcd for $C_{27}H_{34}N_4O_4S$: C, 63.51; H, 6.71; N, 10.97. Found: C, 63.45; H, 6.53; N, 10.96.

The free biuret **15** was obtained on treating a solution of 10.20 g (0.02 mol) of **12** in 50 ml of dichloromethane with dry hydrogen chloride gas for 1 h. The residue obtained after evaporating the solvent was treated with methanol leaving colorless plates of **15**, which were filtered off and washed with methanol: 7.4 g (90%) of **15**; mp 140 °C (MeOH); ir ($CHCl_3$) 1720, 1680 cm^{-1} (C=O); ^{13}C NMR ($CDCl_3$) δ 153.3 and 150.4 ppm (carbonyl C).

Anal. Calcd for $C_{21}H_{19}N_3O_4S$: C, 61.61; H, 4.68; N, 10.27. Found: C, 61.09; H, 4.76; N, 10.13.

B. From 1,3-Diphenyldiazetidine-2,4-dione (14) and *p*-Toluenesulfonamide. A solution of 0.01 mol of **14**, *p*-toluenesulfonamide, and triethylamine each in 25 ml of chloroform was kept at 80 °C for 23 h while the progress of the reaction was followed by ir (disappearance of C=O bands of the diazetidine-2,4-dione at 1770 cm^{-1}). The salt **12** was separated from the reaction solution by adding diethyl ether. Thus 2.2 g (43%) of **12** was obtained, identical with a sample prepared under A.

A mixture of 0.01 mol of **14** and *p*-toluenesulfonamide was heated in 10 ml of DMF for 20 h to 120 °C, while the disappearance of **14** was followed by ir. The resulting brown solution yielded, on gradual dilution with water, fractions of 2.2 g of *N,N'*-diphenylurea, mp 245 °C (identical in ir comparison with an authentic sample), and 0.9 g of *N,N*-dimethyl-*N'*-(*p*-toluenesulfonyl)formamidine, mp 134–135 °C (lit.[11] 135–137 °C), ir ($CHCl_3$) 1625 cm^{-1} (C=N).

C. From *N*-Phenyl-*N'*-(*p*-toluenesulfonyl)urea and Phenyl Isocyanate. On adding 0.4 g (0.004 mol) of triethylamine to a suspension of 1.1 g (0.0038 mol) of *N*-phenyl-*N'*-(*p*-toluenesulfonyl)urea in 10 ml of chloroform, salt formation with solvation of the starting material takes place. After 0.45 g (0.0038 ml) of phenyl isocyanate was added the solution was heated to reflux for 3–4 h while the progress of the reaction was followed by ir (disappearance of the –N=C=O band at 2260 cm^{-1}). The resulting solution was diluted with diethyl ether, causing separation of 1.05 g (54%) of **12**, identical with a sample prepared under A.

Registry No.—**1a**, 59812-63-4; **1b**, 59812-64-5; **1c**, 59812-65-6; **1d**, 59812-66-7; **1e**, 59812-67-8; **1f**, 59812-68-9; **2**, 59812-69-0; **3** (R' = *p*-$CH_3C_6H_4$), 59812-79-2; **7**, 59812-80-5; **10a**, 59812-70-3; **10b**, 59812-71-4; **10c**, 59812-72-5; **11a**, 59812-73-6; **11b**, 59812-74-7; **11c**, 59812-75-8; **11d**, 59812-76-9; **11e**, 59812-77-0; **11f**, 59812-78-1; **12**, 59812-82-7; **14**, 1025-36-1; **15**, 59812-81-6; RNCO (R = Me), 624-83-9; RNCO (R = Ph), 103-71-9; RNCO (R = *p*-$CH_3C_6H_4$), 622-58-2; RNCO (R = *m*-$CH_3C_6H_4$), 621-29-4; RNCO (R = *p*-ClC_6H_4), 104-12-1; RNCO (R = $PhCH_2$), 3173-56-6; R'SO_2NCO (R' = *p*-ClC_6H_4), 5769-15-3; R'O_2NCO (R' = *p*-$CH_3C_6H_4$), 4083-64-1; R'SO_2NH_2 (R' = Ph), 98-10-2; R'SO_2NH_2 (R' = *p*-$CH_3C_6H_4$), 70-55-3; 1,2-dimethylimidazole, 1739-84-0; *N*-methyl-*N'*-(*p*-toluenesulfonyl)urea, 13909-69-8; *N*-phenyl-*N'*-(*p*-toluenesulfonyl)urea, 13909-63-2; *N,N'*-diphenylurea, 102-07-8.

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Fluoroxytrifluoromethane Reactions with Polynuclear Arenes. A New Route to Fluorinated K-Region Ketones

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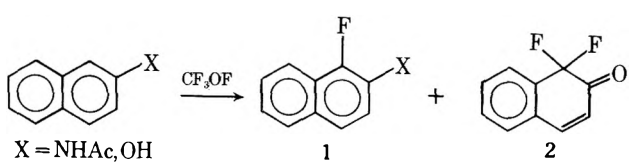
Reactions between 9-(*N*-acetylamino)phenanthrene (**3**), 5-(*N*-acetylamino)benzo[*c*]phenanthrene (**5**), 5-methoxy-7,12-dimethylbenz[*a*]anthracene (**7**), and fluoroxytrifluoromethane (CF_3OF) yielded 10,10-difluorophenanthren-9(10*H*)-one (**4**, 40%), 6-fluorobenzo[*c*]phenanthren-5(6*H*)-one (**6**, 30%), and 6-fluoro-7,12-dimethylbenz[*a*]anthracen-5(6*H*)-one (**8**, 45%), respectively, as the major products. Compounds **6** and **8** were found to exist predominantly as the K-region ketone instead of the usual K-region phenol; steric and fluorine electronic effects are used to explain the preference for the ketonic tautomer.

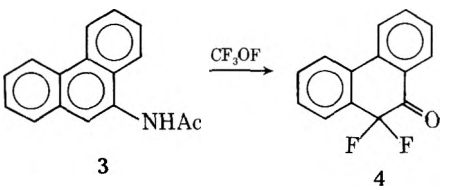
Previous work on fluoroxytrifluoromethane (CF_3OF) reactions with polynuclear aromatic systems has revealed reactions which include monofluorination, *gem*-difluorination, and oxidation.[2] Thus certain 2-substituted naphthalene derivatives reacted with CF_3OF to produce 1-fluoro substituted naphthalenes (**1**) and 1,1-difluoronaphthalen-2(1*H*)-one (**2**).



9-Substituted anthracenes produced only the oxidation product anthraquinone. Further studies of CF_3OF reactions with higher polynuclear arenes were pursued to determine (1) the orientation and extent of fluorination, (2) the synthetic utility, and (3) the properties of the derived products.

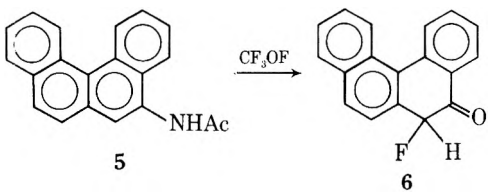
Results

9-(*N*-Acetylamino)phenanthrene (**3**) reacted with CF_3OF in chloroform solution at room temperature to yield a mixture of 9,10-phenanthraquinone (3%), 10,10-difluorophenanthren-9(10*H*)-one (**4**, 40%), and an unidentified high-melting



material. No evidence was obtained for the presence of a monofluorination product. The *gem*-difluoro ketone **4** shows carbonyl absorption in the infrared spectrum at 1700 cm^{-1}; compound **2** had previously been observed to contain absorption at 1700 cm^{-1} for the carbonyl group.[2]

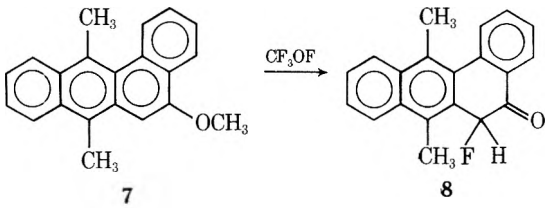
The reaction between CF_3OF and 5-(*N*-acetylamino)benzo[c]phenanthrene (5) produced a dark oil which, after several chromatographic purifications, furnished 6-fluorobenzo[c]-phenanthren-5(6*H*)-one (6) in 30% yield. Compound 6 showed



5 6

carbonyl absorption in its infrared spectrum at 1720 cm^{-1}; no hydroxyl absorption was observed.

When 5-methoxy-7,12-dimethylbenz[a]anthracene (7) and CF_3OF were allowed to react, the major identifiable product, isolated in 45% yield, was 6-fluoro-7,12-dimethylbenz[a]-anthracen-5(6*H*)-one (8). Compound 8 displayed carbonyl



7 8

absorption at 1700 cm^{-1} and some detectable hydroxyl absorption at 3390 cm^{-1}.

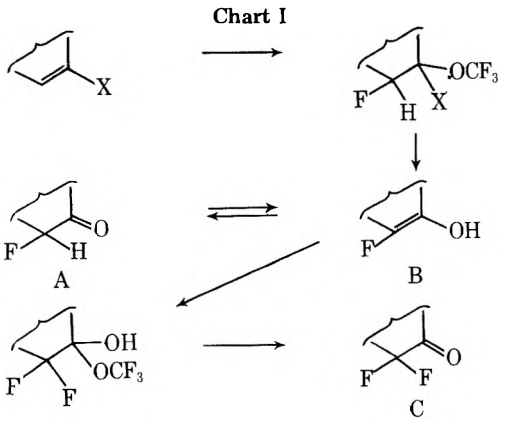
A material balance of 80–100% was found in all reactions with intractable, high-melting material accounting for the unidentified portion of the reactions. In the case of 7, an empirical formula for the material was determined from elemental analysis as C_5H_3OF; the material did not have enough volatility for a mass spectral investigation.

Fluoroxy reactions with several unsubstituted polynuclear aromatic systems were also attempted. Naphthalene and phenanthrene were found unreactive; benz[a]anthracene afforded a small amount of viscous oil with an empirical formula of $C_{18}H_{12}F_8$ but structure elucidation has been unsuccessful; anthracene was converted into anthraquinone in 70% yield.

Discussion

Fluoroxytrifluoromethane is a powerful reagent for effecting electrophilic fluorination, addition, and oxidation.[3] The present findings can be interpreted as combined electrophilic substitution–oxidation processes. However, an addition–oxidation path as shown in Chart I is also attractive (X = NHAc, OCH_3).

Chart I



In this path, the K-region bond undergoes addition of CF_3OF followed by oxidation to the fluoro ketone A which is in equilibrium with the fluorophenol B. A steric effect in 6 and 8 renders the K region relatively olefinic in nature.[4] The fluorine atom destabilizes the olefin-like[5] system such that the keto form predominates and reaction stops at this point. In the absence of the steric effect, the K-region phenolic tautomer (B) predominates and a second addition occurs; subsequent oxidation affords the α,α-difluoro ketone C. Previous results with 2-naphthol show that both the monofluorophenol and α,α-difluoro ketone can be isolated: the aromatic character of the naphthalene system possibly retards the addition reaction. The ir and NMR spectra of 6 and 8 show that the keto structure is highly predominant in 6 while 8 contains a small but detectable (ir) amount of phenol tautomer.

Keto tautomers have previously been reported present in significant amount in 5-hydroxy-[4,6] and 6-hydroxy-7,12-dimethylbenz[a]anthracene (DMBA).[7] The 5-hydroxy isomer exists in approximately 1:1 equilibrium with its ketonic tautomer.[4] The dominance of the keto form in both 6 and 8 can be explained using a combination of steric and fluorine electronic effects. The close proximity of two fused benzene rings in benzo[c]phenanthrene renders the system nonplanar;[8] the K region thus loses some resonance stabilization and gains olefinic character. Substitution of a fluorine atom in the K region destabilizes the olefinic bond through electron repulsion[5] thus causing 6 to exist in the keto form. 5-Hydroxybenzo[c]phenanthrene, without the fluorine substituent, exists as the phenolic tautomer.[9] Similar reasoning for increased olefinic character of the K region in 5-hydroxy-DMBA, which has internal strain from the interaction of the 12-methyl group and the 1 proton,[10] has been evoked.[4] 5-Hydroxybenz[a]-anthracene, without the steric crowding, exists as the phenolic tautomer.[6] Thus the strain in 5-hydroxy-DMBA accounts for the increased ketone content and the fluorine substituent effect in 6-fluoro-5-hydroxy-DMBA (8) can explain the dominance of the keto tautomer in this system.

The K-region keto structure has been suggested as an important intermediate in the carcinogenic activity of DMBA.[4] Although initial carcinogenic activity tests have not supported this suggestion,[7] thorough testing of the suggestion has not been completed. The reactions between CF_3OF and the polynuclear arenes described in this study constitute a novel route to K-region ketones. More in-depth study of K-region ketones and their role in carcinogenic activity is now possible.

Experimental Section

All temperature readings are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. NMR spectra were determined on a Varian T-60 spectrometer using tetramethylsilane (δ 0.0) as an internal standard. Mass spectra were obtained on a Varian MAT-111 spectrometer (80 eV); samples were introduced using a direct inlet probe. Infrared spectra were determined on a Perkin-Elmer Model 337 grating spectrophotometer using polystyrene for calibration. Fluoroxytrifluoromethane was obtained from PCR, Inc., Gainesville, Fla., or prepared according to literature procedures.[11] Reagent grade chloroform was used in all reactions. TLC was performed using Mallinkrodt SilicAR.

General Procedure. 10,10-Difluorophenanthren-9(10*H*)-one (4). To a solution of 9-(*N*-acetylamino)phenanthrene[12] (0.25 g, 1.06 mmol) in 75 ml of chloroform contained in a 200-ml, round-bottomed flask open to the atmosphere was added with stirring at ambient temperature a slow stream of CF_3OF gas (9.6 mmol) until TLC analysis showed only a trace of starting material remaining (1 h). The contents were then stirred and nitrogen gas was used to facilitate the removal of excess CF_3OF. A white, high-melting (>400 °C) substance, 0.075 g, was removed by filtration.

The concentrated filtrate was chromatographed on a 26.5 × 2.5 cm Florisil column (benzene) yielding, after sublimation and recrystallization (hexane), 87.3 mg (40%) of slightly yellow 4: mp 100–102 °C; ir (KBr) 1700 cm^{-1} (C=O); NMR (CCl_4) δ 7.2–8.1 (aromatic); MS *m/e* (rel intensity) 230 (M, 92), 211 (92), 200 (100). Anal. Calcd for $C_{14}H_8F_2O$: C, 73.1: H, 3.5; F, 16.4. Found: C, 73.4; H, 3.6; F, 16.4.

Chloroform eluent furnished 12.5 mg (6.3%) of 9,10-phenanthraquinone identified by comparison with authentic material, mp 205 °C (lit.[13] mp 208.5–210 °C). Further elution gave 65 mg of unreacted **3**.

A reaction attempted at −20 °C gave only unchanged starting material.

6-Fluorobenzo[*c*]phenanthren-5(6*H*)-one (6). A solution of 0.21 g (0.72 mmol) of 5-(*N*-acetylamino)benzo[*c*]phenanthrene[14] in 75 ml of chloroform was treated with 2.4 g of CF_3OF according to the above procedure. After removal of residual gas and concentration on a rotary evaporator, 0.34 g of crude oil was obtained. Preparative TLC (500 μ, 20 × 5 cm slide, $CHCl_3$) showed the presence of several substances from which the major component **6** (R_f 0.39) was isolated as an oil (57.7 mg, 30%) which slowly crystallized over a period of 2 months: mp 85–88 °C (yellow crystals); ir (neat) 1730 (C=O), 730 cm^{-1}; NMR ($CDCl_3$) δ 4.43 (1 H, benzylic proton, d, J_{HF} = 48 Hz), 7.4–8.0 (10 H, m, aromatic); MS *m/e* (rel intensity) 262 (M, 100), 243 (14), 232 (21), 149 (38). Anal. Calcd for $C_{18}H_{11}FO$: C, 82.4; H, 4.2; F, 7.3. Found: C, 82.1; H, 4.5; F, 7.7.

6-Fluoro-7,12-dimethylbenz[*a*]anthracen-5(6*H*)-one (8). 6-Methoxy-7,12-dimethylbenz[*a*]anthracene[15] (0.25 g, 0.66 mmol) in 75 ml of chloroform was reacted with 1.0 g of CF_3OF. A brown solid (0.059 g) was obtained by filtration: mp >400 °C; empirical formula, C_5H_3FO; mass spectrum not attainable owing to low volatility; ir (KBr) broad, diffuse absorptions.

The concentrated filtrate furnished a dark oil which gave four fractions by TLC (300 μ, 20 × 5 cm, 1:1 $CHCl_3$–hexane): (1) R_f 0.074, 9.1 mg, identical with above described high melting point material; (2) R_f 0.50, 26 mg, unidentified; (3) R_f 0.79, 87 mg (45%) of **8**; (4) R_f 0.95, 59 mg, recovered **7**.

Compound **8** gave the following properties: mp 159–160 °C; ir (KBr) 3390 (OH), 1700 (C=O), 890, 745, 710 cm^{-1} (aromatic); NMR ($CDCl_3$) δ 1.42 (3 H, s, 7-CH_3), 2.88 (3 H, s, 12-CH_3), 4.0 (1 H, d, benzylic, J_{HF} = 84 Hz), 7.3–8.2 (8 H, m, aromatic); MS *m/e* (rel intensity) 290 (M, 7), 275 (22), 271 (7), 260 (100), 245 (50). Anal. Calcd for $C_{20}H_{15}FO$: C, 82,8; H, 5.2; F, 6.6 Found: C, 83.0; H, 5.2; F, 6.5.

Fraction 2 showed a broad melting range of 140 to >300 °C. Analytical TLC indicated the presence of **8** and the substance(s) in fraction 1.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. M.H.L. was supported by a research assistantship from the Graduate School, Southern Illinois University.

Registry No.—**3**, 4235-09-0; **4**, 59830-28-3; **5**, 4176-51-6; **6**, 59830-29-4; **7**, 53306-03-9; **8**, 59830-30-7; CF_3OF, 373-91-1.

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2,4-Dihydroxyphenanthrenes and Derived Ethers. Regioselective Etherification of Acetates

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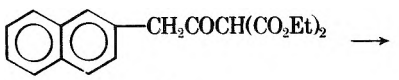
Etherification of the two phenanthrene diacetates **3** and **11** using a large alkyl halide in the presence of anhydrous K_2CO_3 in refluxing dry acetone is much more regioselective at the 2 position than is the direct alkylation of the monosodium salts of the corresponding phenanthrenediols **2** and **10**. However, this regioselectivity unaccountably disappears when methyl iodide is used as the alkylating agent. Also, when the steric hindrance provided by the 5 position is diminished by conversion to the nonplanar 9,10-dihydrophenanthrene system, regioselective etherification of the diacetate (i.e., **20**) no longer occurs. End products of the present work were prepared as carbocyclic analogues of the cannabinoids. Although none shows appreciable central nervous system activity, some of the chemistry used in their preparation may be useful for the syntheses of certain antifungal phytoalexins which are known to be ethers of 2,4-dihydroxy-9,10-dihydrophenanthrenes.

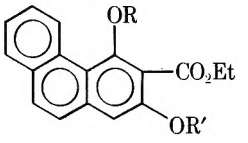
In extension of our work[1] in the cannabinoid field, some 2,4-disubstituted phenanthrenes and corresponding 9,10-dihydro derivatives were prepared as carbocyclic analogues of the pharmacologically potent heterotricyclic substances. Although none of the analogues exhibited appreciable central nervous system activity, some of the chemistry described here should be applicable to improved syntheses in the area of the antifungal phytoalexins, orchinol, hircinol, and loroglossol. These have been shown to be methyl ethers of 9,10-dihydro-2,4,5(7)-trihydroxyphenanthrene.[2,3]

The key intermediate **2** for this work was provided by a modification of a reported method.[4] By treating crude keto ester **1** with methanesulfonic acid at room temperature instead of polyphosphoric acid at 150 °C, the 6% reported yield of **2** was increased to nearly 60%.

Selective ether formation at the less hindered 2 position of **2** was initially approached by simple alkylation of the monosodium salt in hexamethylphosphoramide (HMPA). Under these conditions 3-*p*-fluorophenylpropyl bromide (3-FPB) gave a 53% yield of the desired monoether **4** and a 34% yield of the diether **6**. Column chromatography was necessary for the isolation of both products even though none of the mo-



1



2, R = R′ = H

3, R = R′ = COMe

4, R = H; R′ = $(CH_2)_3$—C$_6$H$_4$—F

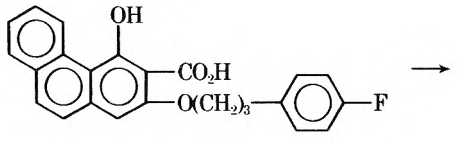
5, R = COMe; R′ = $(CH_2)_3$—C$_6$H$_4$—F

6, R = R′ = $(CH_2)_3$—C$_6$H$_4$—F

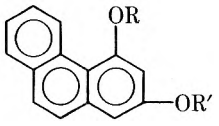
7, R = COMe; R′ = n-C_8H_{17}

8, R = COMe; R′ = CH_2Ph

noether isomeric with **4** was detected in the reaction mixture. Hydrolysis of **4** gave the corresponding acid **9** which could be smoothly decarboxylated to **12.**



9



10, R = R′ = H

11, R = R′ = COMe

12, R = H; R′ = $(CH_2)_3$—C$_6$H$_4$—F

13, R = $(CH_2)_3$—C$_6$H$_4$—F; R′ = H

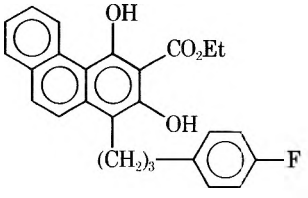
14, R = H; R′ = n-C_8H_{17}

15, R = COMe; R′ = $(CH_2)_3$—C$_6$H$_4$—F

16, R = COMe; R′ = n-C_8H_{17}

17, R = R′ = n-C_8H_{17}

Alkylation of the monosodium salt of 2,4-dihydroxyphenanthrene (**10**) with 3-FPB in HMPA led to only a 35% yield of the monoether **12** plus a 4.7% yield of the isomeric ether **13** as the only other isolable product. The diether, which must have been formed in appreciable amounts, was not isolated in pure form. An incidental observation possibly accounting partly for the less than satisfactory course of this direct alkylation method was encountered when an attempt was made to alkylate the disodium salt of **2** with 3-FPB in HMPA.



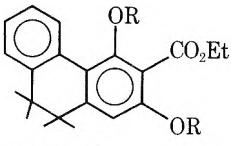
18

Under these conditions the only product isolated was a poor yield (21%) of the carbon-alkylated derivative **18.** Subsequent NMR experiments clearly showed that the proton at the 1 position in **2** undergoes deuterium exchange in Me_2SO-d_6 to which sodium hydride is added.

Attention was next turned to the possibility of selective etherification of the diacetates **3** and **11** using a process discovered by Jurd in connection with regioselective alkylations of polyhydroxyflavones[5] and -flavonols,[6] and later extended to dihydroxycoumarins by Seshadri and coworkers[7]. Thus, when the diacetate **3** was heated under reflux in dry acetone for 77 h with excess 3-FPB in the presence of excess anhydrous K_2CO_3, an 85% yield of the desired ether acetate **5** was secured. In contrast, identical treatment of the corresponding dihydroxy compound **2** led to a quantitative yield of the diether **6.** When n-octyl bromide was used in place of 3-FPB, the crude ether acetate **7** was obtained in good yield and, without purification, was saponified and decarboxylated to the monoether **14** in a 26% overall yield. Likewise, the alkylation of **3** with benzyl chloride produced a 78% yield of the regioselective alkylation product **8.**[8] Most surprisingly, however, methyl iodide in this reaction gave a mixture containing approximately equal amounts of all three possible products: the two monoethers and the dimethyl ether. In view of the fact that methyl iodide was the reagent most often employed by the previous workers,[5-7] its total lack of regioselectivity in the present system is most puzzling.

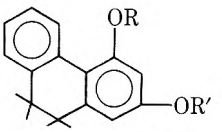
In the diacetate **3,** as in most of the systems studied previously,[5-7] the phenoxide ion leaving group is stabilized by an electronegative group in conjugation with it (i.e., the 3-carbethoxy group in **3**). Nevertheless, when the diacetate **11,** lacking this stabilizing feature, was treated with a larger excess (5:1 vs. 2:1 for the reaction with **3**) of 3-FPB, a 77% yield of the ether acetate **15** was obtained after 75 h of heating under reflux in acetone. However, the reaction with an even larger excess of n-octyl bromide required 114 h to approach the point of completion. Under these conditions, a 76% yield of the ether acetate **16** was isolated along with a 13% yield of the diether **17.** Thus, the absence of the activating group (CO_2Et) appears to reduce the rate but not the regioselectivity of this reaction system.

Hydrogenation of several of these phenanthrenes to their corresponding 9,10-dihydro derivatives was accomplished by a modification of a reported[3] method using palladium–charcoal catalyst and ethyl acetate as solvent. We found that hydrogenation occurred more rapidly in the presence of a small amount of 10% $HClO_4$ in acetic acid. In this way **19** and **20** were obtained from **2** and **3,** respectively; and **21, 22,** and **23** were derived in turn from **12, 15,** and **16.**



19, R = H

20, R = COMe



21, R = H; R′ = $(CH_2)_3$—C$_6$H$_4$—F

22, R = COMe; R′ = $(CH_2)_3$—C$_6$H$_4$—F

23, R = COMe; R′ = n-C_8H_{17}

Finally, it is of interest to note that when the diacetate **20** was treated with 3-FPB in acetone–K_2CO_3, a complex mixture was produced in which **22** was only one of the components. Apparently, the out-of-plane conformation of the two benzene rings in **20** reduces the steric effect of the 5-hydrogen atom on the 4-acetate to the point where attack at the 2-acetate group is no longer favored.[9]

Experimental Section

All melting points were taken in capillary tubes and are uncorrected. Ir spectra (all in $CDCl_3$ solution) were obtained using a Perkin-Elmer Model 521 spectrophotometer. NMR spectra (all in $CDCl_3$ solution) were recorded using a Varian T-60 spectrometer. Chemical shifts are reported as δ relative to tetramethylsilane (δ 0.0 ppm) using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Thin layer chromatograms (TLC) were carried out on Adsorbil-2 silica gel to a distance of 5 cm on microscope slides. Spots were detected by development with iodine vapor.

Ethyl 2,4-Dihydroxy-3-phenanthrenecarboxylate (2). To 400 ml of methanesulfonic acid cooled to 10–15 °C in an ice bath was added with stirring over a period of several minutes 85.5 g of crude 2-naphthylacetylmalonic ester **1**.[4,10] The mixture was stirred at room temperature for 18 h, then poured into 3 l. of water and vigorously stirred for 4 h. Solid product was collected at the filter, and taken up in methylene chloride (400 ml), washed once with 5% $KHCO_3$ (150 ml), and dried over $MgSO_4$. Filtration and removal of solvent by distillation left a yellow solid which was stirred vigorously for 45 min with pentane (200 ml). Collection at the filter afforded 53.7 g of crude product, mp 107–113 °C. One recrystallization from ethanol (700 ml) gave 42.7 g (58% yield based on pure starting material): mp 119–121 °C (lit.[4] mp 115–116 °C); ir 3460, 3370 (OH), 1675 cm^{-1} (bonded C=O); NMR δ 12.54 (s, 1, OH), 9.7–9.4 (m, 1, 5-H), 9.00 (s, 1, OH), 7.8–7.2 (m, 5, 6, 7, 8, 9, 10-H), 6.82 [s, 1, 1-H (exchangeable in Me_2SO-d_6 + NaH)], 4.54 (q, 2, J = 7 Hz, OCH_2CH_3), and 1.42 ppm (t, 3, J = 7 Hz, OCH_2CH_3).

Ethyl 2,4-Diacetoxy-3-phenanthrenecarboxylate (3). By heating a pyridine solution of **2** under reflux (2 h) in the presence of excess acetic anhydride there was obtained a 93% yield of **3**: mp 134–135 °C (ethanol); ir 1780, 1725 cm^{-1} (C=O); NMR δ 9.2–8.8 (m, 1, 5-H), 8.0–7.3 (m, 6, ArH), 4.43 (q, 2, J = 7 Hz, OCH_2CH_3), 2.47 (s, 3, $COCH_3$), 2.33 (s, 3, $COCH_3$), and 1.40 ppm (t, 3, J = 7 Hz, OCH_2CH_3).

Anal. Calcd for $C_{21}H_{18}O_6$: C, 68.84; H, 4.95. Found: C, 68.95; H, 4.89.

Ethyl 2-(3-*p*-Fluorophenylpropoxy)-4-hydroxy-3-phenanthrenecarboxylate (4) and Ethyl 2,4-Di-(3-*p*-fluorophenylpropoxy)-3-phenanthrenecarboxylate (6). To a cold (5 °C), stirred solution of 14.1 g (0.05 mol) of **2** and 14.0 g (0.064 mol) of 3-*p*-fluorophenylpropyl bromide[1,11] in 70 ml of hexamethylphosphoramide (HMPA) was added in nine portions over a period of 5 h 2.5 g (0.06 mol) of sodium hydride (as a 57% dispersion in mineral oil). Stirring at room temperature was continued for 57 h and the neutral reaction mixture was poured into cold water (300 ml). The precipitated oil was taken up in ether (250 ml), washed with water (150 ml), and dried over $MgSO_4$. Filtration and removal of the solvent by distillation left 25.1 g of an oil which was chromatograhed on a silica gel column (6 × 100 cm) using 4 l. of benzene for elution, and monitoring the eluate using TLC (50 C_6H_6–50 CCl_4). Four fractions were obtained: 0.19 g of an oil, 9.54 g of yellow oil (34% yield of 6), 8.67 g of yellow solid, mp 95–100 °C, and 1.62 g of yellow solid, mp 90–95 °C (10.29 g, 53% yield of **4**). Recrystallization of a sample of the solid from ethanol gave pure **4**: mp 102–103 °C; NMR δ 10.67 (s, 1, OH), 9.7–9.2 (m, 1, 5-H), 8.0–6.8 (m, 10, ArH), 4.49 (q, 2, J = 7Hz, OCH_2CH_3), 3.90 (t, 2, J = 6 Hz, OCH_2CH_2), 3.0–2.0 (m, 4, CH_2CH_2Ar), and 1.38 ppm (t, 3, J = 7 Hz, OCH_2CH_3).

Anal. Calcd for $C_{26}H_{23}FO_4$: C, 74.63; H, 5.54. Found: C, 74.89; H, 5.65.

After standing for a month, the 9.54 g of yellow oil began to crystallize. Trituration with hexane completed the solidification. Filtration and washing with pentane yielded 7.02 g of pure **6**: mp 63–65 °C; ir no OH, 1740 cm^{-1} (C=O); NMR δ 9.7–9.2 (m, 1, 5-H), 8.0–6.7 (m, 14, ArH), 4.46 (q, 2, J = 7 Hz, OCH_2CH_3), 4.05 (t, 4, J = 6 Hz, OCH_2CH_2), 3.0–1.7 (m, 8, CH_2CH_2Ar), and 1.37 ppm (t, 3, J = 7 Hz, OCH_2CH_3).

Anal. Calcd for $C_{35}H_{32}F_2O_4$: C, 75.79; H. 5.82. Found: C, 75.50; H, 5.85.

Ethyl 2,4-Dihydroxy-1-(3-*p*-fluorophenylpropyl)-3-phenanthrenecarboxylate (18). To a stirred cold (5 °C) solution of 1.41 g (0.005 mol) of **2** in 5 ml of HMPA was added 0.42 g (0.01 mol) of sodium hydride. After stirring at room temperature for 1.5 h, a solution of 1.09 g (0.005 mol) of 3-p-fluorophenylpropyl bromide was added and stirring was continued for another 19 h. The reaction mixture was worked up as before to give 1.36 g of crude oil which was separated into four fractions by silica gel chromatography (benzene solvent): 0.01 g of yellow oil, 0.40 g of pale yellow solid, mp 110–125 °C (21% yield of impure **18**), 0.10 g of yellow oil, and 0.70 g of yellow oil. One recrystallization of the solid fraction from cyclohexane (10 ml) followed by another from benzene (1 ml)–ethanol (3 ml) gave pure **18** (0.17 g, mp 145–146 °C): ir 3450, 3370 (OH), and 1660 cm^{-1} (C=O); NMR δ 12.30 (s, 1, OH), 9.8–9.4 (m, 1, 5-H), 9.55 (s, 1, OH), 8.0–6.7 (m, 9, ArH), 4.59 (q, 2, J = 7 Hz, OCH_2CH_3), 3.3–2.5 (m, 4, $ArCH_2C$-CH_2Ar), 2.3–1.2 (m, 2, ArC-CH_2-CAr), and 1.45 ppm (t, 3, J = 7 Hz, OCH_2CH_3).

Anal. Calcd for $C_{26}H_{23}FO_4$: C, 74.63; H, 5.54. Found: C, 74.55; H, 5.54.

Ethyl 4-Acetoxy-2-(3-*p*-fluorophenylpropoxy)-3-phenanthrenecarboxylate (5). A stirred mixture of 1.1 g (0.003 mol) of the diacetate **3**, 1.3 g (0.006 mol) of 3-*p*-fluorophenylpropyl bromide, 1.5 g of anhydrous K_2CO_3, a few crystals of KI, and 10 ml of acetone (dried over anhydrous K_2CO_3) was heated under reflux for 77 h. TLC (99 C_6H_6–1 CH_3OH) indicated the presence of only a trace of **3** remaining. Insoluble salts were removed by filtration and washed with acetone. The combined filtrate and washings were concentrated to dryness on a rotary evaporator. Trituration of the residual oil (1.75 g) with pentane produced a solid product which was collected at the filter, washed with pentane, and dried to give 1.18 g (85% yield) of **5**, mp 107–110 °C. One recrystallization from ethanol (8–10 ml) gave pure **5**, mp 110–112 °C, identical (mixture melting point and NMR) with a sample prepared by acetylation of **4** in pyridine–acetic anhydride: NMR δ 9.7–9.3 (m, 1, 5-H), 8.2–6.8 (m, 10, ArH), 4.43 (q, 2, J = 7 Hz, OCH_2CH_3), 4.05 (t, 2, J = 6 Hz, OCH_2CH_2), 3.0–1.8 (m, 4, CH_2CH_2Ar), 2.27 (s, 3, $COCH_3$), and 1.35 ppm (t, 3, J = 7 Hz, OCH_2CH_3).

Anal. Calcd for $C_{28}H_{25}FO_5$: C, 73.03; H, 5.47. Found: C, 73.22; H, 5.46.

Subjecting the dihydroxy derivative **2** to the foregoing conditions produced no detectable amounts of the monoether (i.e., **4**). Instead, essentially a quantitative yield of the diether **6** was obtained.

Ethyl 4-Acetoxy-2-*n*-octyloxy-3-phenanthrenecarboxylate (7). A stirred mixture of 7.3 g (0.02 mol) of **3**, 19.3 g (0.1 mol) of *n*-octyl bromide, 20 g of anhydrous K_2CO_3, 1 g of KI, and 90 ml of dry acetone was heated under reflux for 64 h and worked up as in the foregoing procedure. A brown oil (8.93 g) was obtained which did not crystallize: NMR δ 9.6–9.2 (m, 1, 5-H), 8.0–7.3 (m, 6, ArH), 4.46 (q, 2, J = 7 Hz, OCH_2CH_3), 4.00 (t, 2, J = 6 Hz, OCH_2CH_2), 2.27 (s, 3, $COCH_3$), and 2.5–0.5 ppm (m, 20.5 instead of 18, C-CH). The high integration in the aliphatic C-CH region suggested the presence of octyl bromide or octanol as impurity. However, this material was usable in the next step without further purification.

Ethyl 4-Acetoxy-2-benzyloxy-3-phenanthrenecarboxylate (8). Treatment of **3** with excess benzyl chloride for 70 h in boiling acetone in the presence of anhydrous K_2CO_3 gave a 78% yield of **8**: mp 71–72 °C (from hexane); NMR δ 9.7–9.3 (m, 1, 5-H), 8.0–7.2 (m, 11, ArH), 5.03 (s, 2, $OCH_2C_6H_5$), 4.38 (q, 2, J = 7 Hz, OCH_2CH_3), 2.27 (s, 3, $COCH_3$), and 1.27 ppm (t, 3, J = 7 Hz, OCH_2CH_3).

Anal. Calcd for $C_{26}H_{22}O_5$: C, 75.34; H, 5.35. Found: C, 75.04; H, 5.35.

Reaction of 3 with Excess CH_3I. When the diacetate **3** was treated with excess CH_3I for 54 h in the usual manner, a quantitative yield of a pale yellow glass was obtained. TLC (99 C_6H_6–1 CH_3OH) showed that it contained three components (R_f 0.52, 0.62, and 0.75) none of which was **3** (R_f 0.37). The 60-Hz NMR spectrum of this material disclosed the presence of two acetyl methyl groups (2.30 and 2.42 ppm) and the 100-Hz NMR spectrum (recorded on a Varian Associates HA-100 spectrometer) revealed the presence of three *O*-methyls (3.90, 3.92, and 3.94 ppm). From the integral values of these five peaks it could be determined that the mixture consisted of 30% of one monomethoxyacetate derivative, 31% of the other monomethoxyacetate isomer, and 36% of the dimethoxy derivative, in which both acetyl groups of **3** had been displaced.

2-(3-*p*-Fluorophenylpropoxy)-4-hydroxy-3-phenanthrenecarboxylic Acid (9). A mixture of 5.4 g of the ester **4**, 24 g of KOH, 90 ml of water, and 65 ml of ethanol was stirred and heated under reflux in a nitrogen atmosphere for 21 h. The cooled mixture was poured onto ice containing 75 ml of 6 N hydrochloric acid. Precipitated oil was taken up in ether, washed to neutrality with water, and dried over $MgSO_4$. Filtration and removal of the ether by distillation yielded 4.71 g (93%), mp 110–116 °C, sufficiently pure for the next

step. Two recrystallizations of a sample from CCl_4 gave pure **9**: mp 119–120 °C; ir 3400 (broad, bonded OH) and 1690 cm^{-1} (C=O); NMR δ 12.8–12.2 (in, 1, CO_2H), 11.75 (s, 1, ArOH), 9.2–8.7 (m, 1, 5-H), 8.1–6.8 (m, 10, ArH), 4.03 (t, 2, J = 6 Hz, OCH_2CH_2), and 3.0–1.8 ppm (m, 4, C-CH_2CH_2Ar).

Anal. Calcd for $C_{24}H_{19}FO_4$: C, 73.83; H, 4.91. Found: C, 73.83; H, 4.88.

2-(3-*p*-Fluorophenylpropoxy)-4-hydroxyphenanthrene (12). The 4.71 g of crude acid **9** was mixed with 0.5 g of copper power and subjected to distillation in a Kugelrohr under a vacuum of 0.01 mm. At 160–170 °C (air bath temperature) decarboxylation began and the pressure increased to 0.1 mm. As decarboxylation neared completion the pressure decreased again to 0.01 mm and product distilled at 180–240 °C. The solid distillate (4.10 g) was redistilled in the Kugelrohr under the same conditions to give 3.41 g (82%) of product, mp 111–115 °C. Recrystallization of a sample from CCl_4 gave pure **12**: mp 116–117 °C; ir 3620 cm^{-1} (OH); NMR δ 9.9–9.5 (m, 1, 5-H), 8.0–6.5 (m, 11, ArH), 5.3–4.8 (broad, 1, OH),[12] 4.08 (t, 2, J = 6 Hz, OCH_2CH_2), 3.2–2.6 (m, 2, CH_2CH_2Ar), and 2.6–1.8 ppm (m, 2, $CH_2CH_2CH_2$Ar).

Anal. Calcd for $C_{23}H_{19}FO_2$: C, 79.75; H, 5.53. Found: C, 79.87; H, 5.63.

4-(3-*p*-Fluorophenylpropoxy)-2-hydroxyphenanthrene (13). 2,4-Dihydroxyphenanthrene,[4] mp 159–161 °C (from 2-propanol–H_2O), was alkylated with 3-*p*-fluorophenylpropyl bromide in HMPA as described above for the preparation of **4**. The crude product was chromatographed on a silica gel column using $CHCl_3$ for elution. In addition to a 35% yield of the hydroxy ether **12**, mp 115–117 °C, R_f 0.34 ($CHCl_3$), there was obtained a 4.7% yield of the isomeric hydroxy ether **13**: mp 122–124 °C; R_f 0.57 ($CHCl_3$); NMR δ 9.7–9.3 (m, 1, 5-H), 8.2–6.5 (m, 11, ArH), 5.77 (s, 1, OH),[12] 3.97 (t, 2, J = 6 Hz, OCH_2CH_2), 3.0–2.4 (m, 2, CH_2CH_2Ar), and 2.4–1.7 ppm (m, 2, $CH_2CH_2CH_2$Ar).

Anal. Calcd for $C_{23}H_{19}FO_2$: C, 79.75; H, 5.53. Found: C, 79.43; H, 5.51.

4-Hydroxy-2-*n*-octyloxyphenanthrene (14). The 8.93 g of impure acetoxy ester **7** was saponified as described above for the preparation of the acid **9**. The dark colored oil (7.2 g) thus obtained could not be crystallized so it was decarboxylated by the procedure specified previously for the preparation of **12**. Multiple trituration of the crude oily distillate with hexane produced 1.72 g (26% yield from **7**), mp 85–95%. One recrystallization from cyclohexane (60 ml) and another from CCl_4 (5 ml) gave 0.53 g of pure **14**: mp 93–96 °C; NMR δ 9.8–9.3 (m, 1, 5-H), 8.0–7.2 (m, 5, ArH), 6.82 (d, 1, J = 2 Hz, 1- or 3-H), 6.68 (d, 1, J = 2 Hz, 3- or 1-H), 5.8–5.0 (broad, 1, OH), 4.07 (t, 2, J = 6 Hz, OCH_2CH_2), and 2.2–0.3 ppm (m, 15, C-CH).

2,4-Diacetoxyphenanthrene (11). The dihydroxy ester **2** (8 g) was hydrolyzed and decarboxylated according to Hardegger et al.[4] The crude 2,4-dihydroxyphenanthrene (6.25 g, mp 155–160 °C) was directly acetylated in pyridine–acetic anhydride (see preparation of **3** above) to give 8.0 g (96% yield from **2**), mp 137–140 °C, suitable for further use. Recrystallization from methanol produced pure **11**: mp 140–142 °C; ir 1760–1790 cm^{-1} (C=O); NMR δ 9.4–8.8 (m, 1, 5-H), 7.8–6.8 (m, 7, ArH), 2.52 (s, 3, $COCH_3$), and 2.35 ppm (s, 3, $COCH_3$).

Anal. Calcd for $C_{18}H_{14}O_4$: C, 73.46; H, 4.80. Found: C, 73.53; H, 4.81.

4-Acetoxy-2-(3-*p*-fluorophenylpropoxy)phenanthrene (15). A stirred mixture of the diacetate **11** (1.77 g, 0.006 mol), 3-*p*-fluorophenylpropyl bromide (6.5 g, 0.03 mol), 6 g of anhydrous K_2CO_3, a few crystals of KI, and 40 ml of dry acetone was heated under reflux for 75 h. The usual workup led to 1.80 g (77%) of crude product, mp 94–98 °C. Recrystallization from cyclohexane gave 1.40 g of pure **15**, mp 109–110 °C, identical (mixture melting point and NMR) with the product of acetylation of **12**: NMR δ 9.9–9.6 (m, 1, 5-H), 8.0–6.8 (m, 11, ArH), 4.20 (t, 2, J = 6 Hz, OCH_2CH_2), 3.3–2.7 (m, 2, CH_2CH_2Ar), 2.33 (s, 3, $COCH_3$), and 2.7–2.0 ppm (m, 2, $CH_2CH_2CH_2$Ar).

4-Acetoxy-2-*n*-octyloxyphenanthrene (16) and 2,4-Di-*n*-octyloxyphenanthrene (17). A stirred mixture of the diacetate **11** (16.6 g, 0.0562 mol), 8.2 ml of *n*-octyl bromide, 60 g of anhydrous K_2CO_3, 5 g of KI, and 350 ml of dry acetone was heated under reflux for 114 h. The usual workup led to 13.3 g (65%) of **16**, mp 74–76 °C. Recrystallization of a sample from acetone gave pure **16**, mp 76–77 °C, identical (mixture melting point and NMR) with the product of acetylation of **14**: NMR δ 9.7–9.5 (m, 1, 5-H), 8.0–7.3 (m, 5, ArH), 7.22 (d, 1, J = 2 Hz, 1- or 3-H), 6.85 (d, 1, J = 2 Hz, 3- or 1-H), 4.15 (t, 2, J = 6 Hz, OCH_2CH_2), 2.27 (s, 3, $COCH_3$), and 2.2–0 5 ppm (m, 15, C-CH).

Anal. Calcd for $C_{24}H_{28}O_3$: C, 79.08; H, 7.74. Found: C, 79.14; H, 7.84.

A residual pentane-soluble fraction (8.15 g) was chromatographed on a silica gel column (3 × 80 cm). From 3 l. of CCl_4 eluate was obtained 3.23 g (13% yield) of **17**, mp 52–54.5 °C, R_f 0.79 (CCl_4). This was followed by 1 l. of benzene from which was obtained 2.34 g more **16**, mp 70–74 °C, R_f 0.20 (CCl_4), bringing the total yield of **16** to 76% (15.64 g). A sample (0.6 g) of the 3.23 g was recrystallized twice from acetone (1–2 ml) to give pure **17**: mp 56–57.5 °C; NMR δ 9.7–9.5 (m, 1, 5-H), 8.0–7.4 (m, 5, ArH), 6.88 (d, 1, J = 2 Hz, 1- or 3-H), 6.78 (d, 1, J = 2 Hz, 3- or 1-H), 4.4–3.9 (m, 4, OCH_2CH_2), and 2.2–0.5 ppm (m, 30, C-CH).

Anal. Calcd for $C_{30}H_{42}O_2$: C, 82.90; H, 9.74. Found: C, 82.71; H, 9.93.

Ethyl 9,10-Dihydro-2,4-dihydroxy-3-phenanthrenecarboxylate (19). A suspension of 2.8 g of 5% Pd/C in 200 ml of ethyl acetate containing 1.8 ml of 10% $HClO_4$ in glacial HOAc was prehydrogenated for 4 h. Then 2.82 g (0.01 mol) of **2** was added and hydrogenation at room temperature and 3 atm pressure was continued for 7 h after which uptake appeared to be complete. The mixture was filtered from catalyst, washed with bicarbonate solution and water, and dried over Na_2SO_4. Filtration and removal of the solvent by distillation gave a residue which solidified upon trituration with pentane, 2.0 g, mp 68–73 °C. Recrystallization of a sample from ethanol gave pure **19**: mp 71–73 °C; NMR δ 10.90 (s, 1, OH), 9.50 (s, 1, OH), 8.5–8.2 (m, 1, 5-H), 7.5–7.0 (m, 3, ArH), 6.45 (s, 1, 1-H), 4.55 (q, 2, J = 7 Hz, OCH_2CH_3), 2.70 (s, 4, $ArCH_2CH_2Ar$), and 1.27 ppm (t, 3, J = 7 Hz, OCH_2CH_3).

Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.80; H, 5.72.

Ethyl 2,4-Diacetoxy-9,10-dihydro-3-phenanthrenecarboxylate (20). Hydrogenation of 2.6 g of **3** under the above conditions led to a quantitative uptake of hydrogen in less than 2 h. Workup in the usual way gave 2.5 g of pure **20**: mp 113–114 °C (from hexane); NMR δ 8.2–7.7 (m, 1, 5-H), 7.5–7.1 (m, 3, ArH), 6.98 (s, 1, 1-H), 4.31 (q, 2, J = 7 Hz, OCH_2CH_3), 2.73 (s, 4, $ArCH_2CH_2Ar$), 2.22 (s, 3, $COCH_3$), 2.15 (s, 3, $COCH_3$), and 1.28 ppm (t, 3, J = 7 Hz, OCH_2CH_3).

Anal. Calcd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.29; H, 5.51.

9,10-Dihydro-2-(3-*p*-fluorophenylpropoxy)-4-hydroxyphenanthrene (21). Hydrogenation of **12** in the prescribed manner gave **21**: mp 98–99.5 °C; NMR δ 8.5–8.2 (m, 1, 5-H), 7.5–6.8 (m, 7, ArH), 6.32 (s, 2, 1- and 3-H), 4.94 [s (broad), 1, OH], 3.92 (t, 2, J = 6 Hz, OCH_2CH_2) 2.67 (s, 4, $ArCH_2CH_2Ar$), and 3.2–1.7 ppm (m, 4, $CH_2CH_2CH_2Ar$).

Anal. Calcd For $C_{23}H_{21}FO_2$: C, 79.29; H, 6.08. Found: C, 79.01; H, 6.17.

4-Acetoxy-9,10-dihydro-2-(3-*p*-fluorophenylpropoxy)phenanthrene (22). Likewise, hydrogenation of **15** in the same way produced a 90% yield of **22**: mp 72.5–74 °C (from pentane); NMR δ 8.5–8.2 (m, 1, 5-H), 7.5–6.4 (m, 9. ArH), 3.97 (t, 2, J = 6 Hz, OCH_2CH_2), 2.72 (s, 4, $ArCH_2CH_2Ar$), 2.22 (s, 3, $COCH_3$), and 3.0–0.7 ppm (m, 4, $OCH_2CH_2CH_2Ar$).

Anal. Calcd for $C_{25}H_{23}FO_3$: C, 76.90; H, 5.93. Found: C, 77.10; H, 6.01.

4-Acetoxy-9,10-dihydro-2-*n*-octyloxyphenanthrene (23). Similarly, hydrogenation of **16** provided an 80% yield of **23**: mp 79–80 °C (from acetone); NMR δ 8.5–8.2 (m, 1, 5-H), 7.3–7.0 (m, 3, ArH), 6.63 (s, 2, 1- and 3-H), 3.98 (t, 2, J = 6 Hz, OCH_2CH_2), 2.72 (s, 4, $ArCH_2CH_2Ar$), 2.23 (s, 3, $COCH_3$), and 1.8–0.5 ppm (m, 15, C-CH).

Anal. Calcd for $C_{24}H_{30}O_3$: C, 78.65; H, 8.25. Found: C, 78.80; H, 8.42.

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References and Notes

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(8) The 5-benzyloxy derivative of 8 would obviously serve as a useful intermediate for the synthesis of hircinol: 9,10-dihydro-2,5-dihydroxy-4-methoxyphenanthrene.
(9) This steric difference is also evident in the NMR spectra of 20 vs. 3. In 3 the 5 proton is shifted downfield to the 9.5-ppm region, a feature characteristic of the planar phenanthrene ring in which the 5 (and 4) proton is abnormally deshielded by being in the nodal plane of two benzene rings. In 20, the 5 proton appears in the 8-ppm region, almost a normal aromatic chemical shift.
(10) Prepared by the reaction of 2-naphthylacetyl chloride with ethoxymagnesiomalonic ester according to the method of G. Reynolds and C. Hauser, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 708.
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(12) The observation that the OH peak in 12 is broad (8 Hz width at half-height) and in 13 is a sharp singlet is consistent with the expectation that proton exchange (or rotation around the Ar–O– bond) would be slower in 12 owing to the steric effect of the adjacent 5 position.

Selective Cleavage of Aryl Esters by Anhydrous Alkali Carbonates

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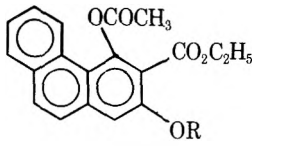
In the presence of a 10% excess of Cs_2CO_3 in either boiling THF (21 h) or boiling DME (10 h), the phenanthrene-2,4-diacetate **1** is converted quantitatively to the corresponding monoacetate **2**. Likewise, in boiling DME (24 h) with 50% excess Cs_2CO_3, dibenzoylresorcinol **4** gives >95% yields of monobenzoylresorcinol **5**. Provided that anhydrous conditions are maintained, no further cleavage of **5** to resorcinol is observed. The conversion of **4** to **5** was studied systematically by using varying quantities of potassium and cesium carbonates and bicarbonates in THF and DME, and by measuring the quantities of evolved CO_2. A mechanism is proposed which accounts for the observed results.

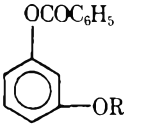
In an accompanying paper, the regioselective etherification of two phenanthrene-2,4-diacetates was described.[1] For example, heating the diacetate **1** under reflux in dry acetone for 77 h with excess 3-*p*-fluorophenylpropyl bromide (3-FPB) in the presence of excess anhydrous K_2CO_3 led to an 85% yield of the monoether **3**.



1, R = $COCH_3$
2, R = H
3, R = $(CH_2)_3$–C$_6$H$_4$–F

In an attempt to reduce the long reaction times required under the heterogeneous conditions involving K_2CO_3, the soluble Cs_2CO_3 was employed instead (Cs_2CO_3 is one of the very few carbonates, if not the only one, showing appreciable solubility in dry acetone). Although the reaction was complete in less than 10 h, the monoether **3** (~60% yield) was contaminated with excessive amounts (~40% yield) of the corresponding diether. When, however, the reaction was carried out in the absence of 3-FPB, a nearly quantitative yield of the monoacetate **2** was isolated after only 5 h (using a 7.4:1 molar ratio of Cs_2CO_3 to **1**). The structure of **2** was established by both ^1H and ^{13}C NMR (see Experimental Section), and by conversion to **3** with 3-FPB. With smaller excess amounts of Cs_2CO_3 in acetone longer reaction times again became necessary. For example, a 2:1 molar ratio gave an 85% yield of **2** only after 48 h. In order to avoid consumption of Cs_2CO_3 by acetone self-condensation reactions which seemed to be occurring, the inert solvents THF and DME were successfully employed instead. Thus, in the presence of only a 10% excess of Cs_2CO_3 a quantitative yield of **2** was obtained after either 21 h of heating under reflux in THF or 10 h in DME. Similarly, a 2:1 molar ratio of $CsHCO_3$ (also appreciably soluble) produced complete conversion of **1** to **2** in 20 h in boiling THF.

To examine further the nature of this aryl ester cleavage, the conversion of resorcinol dibenzoate (**4**) to the corresponding monobenzoate (**5**) was studied in some detail. Re-



4, R = COC_6H_5
5, R = H

actions carried out under various conditions for exactly 24 h were analyzed by NMR to determine the approach to completion, and rough estimates (±5%) were made of the amounts of CO_2 evolved.

In Table IA are summarized the results of heating 0.5 mmol of **4** in boiling THF for 24 h with varying quantities of K_2CO_3 and/or Cs_2CO_3. Comparison of the first three runs clearly shows the beneficial effect of added Cs_2CO_3. However, even a 100% excess of Cs_2CO_3 (run 3) is insufficient to effect complete cleavage in 24 h. It must be noted that when the reactions were carried out under scrupulously anhydrous conditions (runs 1–3) good material balances of **4** and **5** were obtained. When, however, the solvent was not carefully dried (run 4) a poor recovery (68%) was observed. It was established by a separate experiment using TLC for identification that the deficit could be accounted for by further cleavage of **5** to resorcinol which was lost in the aqueous washings during work-up.

Table IB lists the results of similar experiments in boiling DME. Again, the favorable effect of added Cs_2CO_3 is clearly apparent (runs 5–9). When Cs_2CO_3 is used alone, however, up to a 50% excess (run 11) is required to effect total cleavage in the 24-h time limit. Of particular interest is a comparison of run 9 with runs 5 and 10. Run 9, which is a composite of the other two, resulted in yields of both **5** (88%) and CO_2 (52%) which are almost exactly the sum of the corresponding yields

Table I. Carbonate Cleavage of Dibenzoyl- to Monobenzoylresorcinol

$$4\ (0.5\ \text{mmol}) \xrightarrow[\text{THF or DME}]{M_2CO_3} 5 + CO_2\uparrow$$

reflux 24 h

Run no.	K_2CO_3, mmol	Cs_2CO_3, mmol	Yield, % 5	4	CO_2
		A. Solvent THF			
1	3.6	0	18	81	5
2	3.6	0.5	48	51	34
3	0	1.0	58	41	44
4[a]	3.6	0.5	45	23	41
		B. Solvent DME			
5	3.6	0	21	79	11
6	3.6	0.1	41	53	15
7	3.6	0.2	52	43	26
8	3.6	0.3	70	29	38
9	3.6	0.5	88	12	52
10	0	0.55	68	29	42
11	0	0.75	95	0	57
12[b]	0.6	0	29	74	10
13[a]	3.6	0.1	74	12	

[a] Solvent was dried only by passing through a column of basic alumina (activity grade I). [b] Reaction mixture included 0.05 mmol of $C_6H_5CH_2N^+(C_2H_5)_3{\cdot}Cl^-$.

(89% and 53%) of runs 5 and 10. This suggests that the K_2CO_3 and Cs_2CO_3 reactions are essentially independent processes, the former occurring heterogeneously on the surface of the insoluble carbonate, and the latter in solution. Moreover, essentially, no cation exchange between the K_2CO_3 and soluble cesium salts (either Cs_2CO_3 or product salts) can be taking place. This is further supported by the observation (run 12) that a soluble phase-transfer agent has little effect on the K_2CO_3 reaction.

Run 13 again illustrates the damaging effect of moisture. Although the yield (74%) of **5** produced in the 24-h period is higher than that obtained under dry conditions (41% in run 6), the material balance (86%) is poor. Relatively rapid conversion of both **4** to **5** and **5** to resorcino clearly occurs under these conditions.

The high selectivity of the reaction when conducted under completely anhydrous conditions was demonstrated more plainly by means of a preparative run. In the presence of a 35% excess of Cs_2CO_3 in boiling DME, cleavage of **4** to **5** was complete in 16 h, as revealed by TLC. Another 30% excess of Cs_2CO_3 was nevertheless added and the reaction was continued for another 7 h after which there was no indication (TLC) of any change in the composition of the reaction mixture. A 95.5% yield of essentially pure **5** was obtained on workup.

In Table II are listed the results of using potassium and cesium bicarbonates instead of the carbonates in boiling DME. Although an equivalent of $CsHCO_3$ (run 14) produces a good yield (96%) of **5** in the 24-h period, an excess (run 15) gives a lower yield and a poor material balance. Thus, the reaction with bicarbonate clearly does not stop at **5**, even under anhydrous conditions. Also of interest is the observation (run 16) that excess $KHCO_3$ alone gives twice the yield of excess K_2CO_3 (run 5) in the 24-h reaction period. However, neither phase-transfer agents (runs 17, 18) nor a specific potassium ion solvator (run 19) radically improves the $KHCO_3$ reaction even though, unlike K_2CO_3, a uni-univalent salt is here involved.

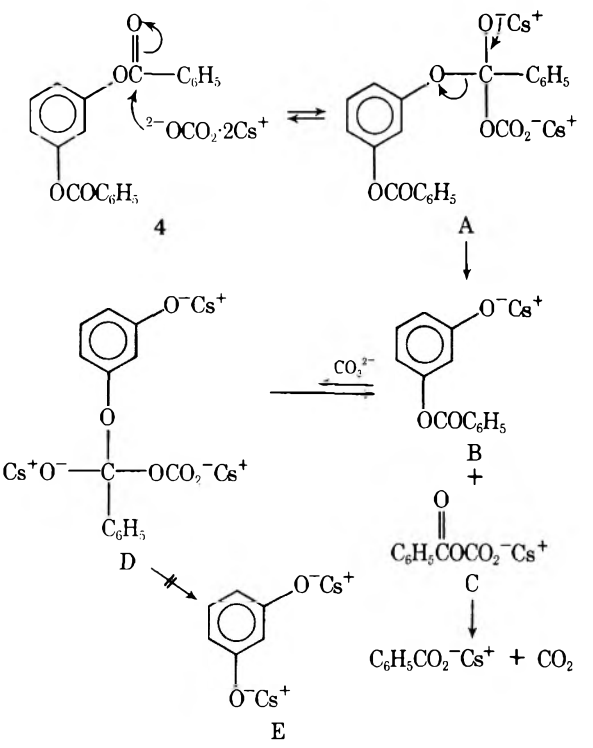
The experimental results described above can be accommodated by the following mechanism.

Table II. Bicarbonate Cleavage of Dibenzoyl- to Monobenzoylresorcinol

$$4\ (0.5\ \text{mmol}) \xrightarrow[\text{DME, reflux 24 h}]{MHCO_3} 5 + CO_2\uparrow$$

Run no.	$KHCO_3$, mmol	$CsHCO_3$, mmol	Yield, % 5	4	CO_2
14	0	0.95	96	0	79
15	0	1.3	68	0	80
16	5.0	0	43	55	41
17[a]	1.2	0	48	51	39
18[b]	1.2	0	41	50	37
19[c]	1.2	0	58	39	57

[a] Reaction mixture included 0.05 mmol of $C_6H_5CH_2N^+(C_2H_5)_3{\cdot}Cl^-$. [b] Included 0.05 mmol of Hyamine 10X. [c] Included 0.1 mmol of dicyclohexyl-18-crown-6 ether.



Carbonate ion attack at a carbonyl carbon atom in **4** leads reversibly to the tetrahedral intermediate A which collapses irreversibly to B, the cesium salt of **5**, plus C, the cesium salt of a mixed benzoic carbonic acid anhydride. Intermediate C undergoes further decomposition to cesium benzoate and CO_2, but in the absence of a proton source, is sufficiently stable to account for the observation (Table I) that the yield of CO_2 is consistently less than the yield of **5**. Further attack of B by carbonate ion is not favored because combination of a monoanion with a dianion is necessarily involved. Moreover, even if a small equilibrium concentration of the resulting intermediate D were formed, it would not collapse rapidly to dicesium resorcylate (E) because the doubly charged anion is a relatively poor leaving group. Hence, under anhydrous conditions, the reaction stops after only one ester group is removed.

However, in the presence of a proton source (H_2O or HCO_3^-), equilibrium concentrations of **5** will be formed from B and attack of carbonate at the second carbonyl group can proceed (runs 4, 13, and 15).

Experimental Section

Reagent grade acetone was dried over anhydrous K_2CO_3. Tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) were dried over

anhydrous K_2CO_3 for several days, then distilled from $LiAlH_4$, and stored over CaH pellets. Finely powdered $KHCO_3$, K_2CO_3, $CsHCO_3$, and Cs_2CO_3 were heated at 240–245 °C[2] for 20 h, allowed to cool in a desiccator over P_2O_5, and stored in stoppered bottles in the same desiccator. Resorcinol dibenzoate was recrystallized from ethanol to constant melting point (117 °C) and dried at 60 °C in vacuo. For the ^1H NMR solvent-shift studies a Varian HA-100 spectrometer was used. ^{13}C NMR spectra were measured on an XL-100-15A/TT-100 spectrometer system in the pulse/Fourier transform mode; 8K data points were used. Off-resonance single frequency decoupling (orsfd) experiments were used to assist in assignments. All ^{13}C NMR spectra were of $CDCl_3$ solutions at ambient temperature and chemical shifts are in parts per million relative to tetramethylsilane. For other general experimental conditions, see ref 1.

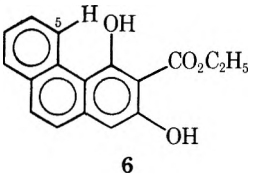
Ethyl 4-Acetoxy-2-hydroxy-3-phenanthrenecarboxylate (2). A stirred mixture of 0.37 g (1 mmol) of ethyl 2,4-diacetoxy-3-phenanthrenecarboxylate (**1**),[1] 2.4 g (7.4 mmol) of Cs_2CO_3, and 20 ml of acetone was heated under reflux for 5 h, at which time TLC (1% CH_3OH in C_6H_6) showed a single spot at R_f 0.75 and nothing at R_f 0.47 corresponding to **1**. The cooled reaction mixture was poured into cold water (200 ml) containing excess HCl. The precipitated solid was collected at the filter, washed with water, and dried to give 0.33 g (100%) of cream-colored powder, mp 148–154 °C. Several recrystallizations from ethanol produced pure **2**: mp 153–154 °C; NMR δ 13.60 (s, 1, OH), 9.8–9.5 (m, 1, 5-H), 8.1–7.4 (m, 5, ArH), 7.03 (s, 1, 1-H), 4.46 (q, 2, J = 7 Hz, OCH_2CH_3), 2.28 (s, 3, $COCH_3$), and 1.37 ppm (t, 3, J = 7 Hz, OCH_2CH_3).

Anal. Calcd for $C_{19}H_{16}O_5$: C, 70.35; H, 4.97. Found: C, 70.13; H, 4.98.

When a similar excess (7.4:1) of dry K_2CO_3 was used instead of the Cs_2CO_3 in the above procedure, reaction was incomplete after 72 h of reflux and NMR analysis of the crude product indicated a 70:30 ratio of **2** to **1**. When Cs_2CO_3 was used in only a 2:1 molar ratio in acetone an 85% yield of **2** was obtainable after 48 h of heating. Yields of 90–100% of **2** were also obtainable under the following sets of conditions: (1) a 1.12:1 molar ratio of Cs_2CO_3 to **1** in refluxing THF for 21 h, (2) a 2:1 molar ratio of $CsHCO_3$ to **1** in boiling THF for 20 h, and (3) a 1.12:1 molar ratio of Cs_2CO_3 to **1** in boiling DME for 10 h.

Ethyl 4-Acetoxy-2-(3-*p*-fluorophenylpropoxy)-3-phenanthrenecarboxylate (3) from 2. To an ice-cold, stirred solution of 0.324 g (1 mmol) of **2** and 0.25 ml (~1.25 mmol) of 3-*p*-fluorophenylpropyl bromide in 2 ml of hexamethylphosphoramide was added 0.046 g (1.1 mmol) of a 57% mineral oil dispersion of sodium hydride. The mixture was stirred at room temperature for 20 h and then poured into cold water (150 ml). Precipitated product was taken up in ether, washed with water, and dried over anhydrous $MgSO_4$. Filtration and concentration to dryness left an oily solid (0.52 g) which was triturated with cold pentane (5 ml), and collected at the filter to give 0.34 g (74%) of **3**, mp 110–113 °C, identical (mixture melting point, TLC, and NMR) with the material, mp 110–112 °C, prepared[1] directly from the diacetate **1**.

^1H NMR Spectral Evidence for the Structure of 2. In preliminary solvent effect experiments, it was found that the peak corresponding to the 5 proton in **6** shifted downfield 0.40 ppm (9.55 to 9.95 ppm) in going from $CDCl_3$ to pyridine-d_5 solution.



6

The corresponding shift in compound **1**, in which an acetate group is near the 5-H, was only 0.18 ppm (9.02 to 9.20 ppm). In **2** this shift was even smaller (9.93 to 9.98 ppm = 0.05 ppm) indicating that the acetate group is also at the 4 position in **2**.

^{13}C NMR Spectral Evidence for the Structure of 2. In the ^{13}C NMR spectrum of compound **6** the hydroxylated C-2 and C-4 carbon atoms can easily be differentiated from the other ring carbons. On the basis of resonance assignments for phenanthrene itself[4] combined with known substituent shifts for benzene,[5] the lower field resonance (163.6 ppm) could be assigned to C-2 and the other (155.7 ppm) to C-4. In the diacetate **1**, both peaks shift upfield to 148.0 and 145.8 ppm, respectively. In the monoacetate **2**, only the C-4 peak shifts upfield to 147.0 ppm. The C-2 peak in **2** actually shifts slightly downfield to 165.2 ppm, again indicating that the hydroxyl group is attached to C-2 and the acetate to C-4.

Resorcinol Monobenzoate (5) from Resorcinol Dibenzoate (4). A stirred mixture of 1.6 g (5 mmol) of **4**, 2.2 g (6.75 mmol) of Cs_2CO_3, and 15 ml of DME was heated under reflux for 16 h. Although TLC (0.5% CH_3OH in C_6H_6) indicated that the reaction was complete, another 0.5 g (1.5 mmol) of Cs_2CO_3 was added and heating was continued for another 7 h. TLC indicated that no change in composition of the reaction mixture occurred during this additional period. The mixture was concentrated to dryness under a stream of dry nitrogen, and ice was added to the pink solid, followed by an excess of 6 N HCl and ether. The ether layer was separated and washed with 2 N $KHCO_3$ (2 × 20 ml). Acidification of the bicarbonate extract precipitated 0.34 g (56% of theory) of benzoic acid, mp 124–125 °C. The ether layer was washed with water to neutrality and dried over anhydrous $MgSO_4$. Filtration and removal of the ether by distillation gave 1.05 g (95.5% yield) of good quality **5**, mp 133–136 °C (lit.[3] mp 135–136 °C).

When the foregoing reaction was conducted in boiling acetone for 24 h using a 2:1 molar ratio of Cs_2CO_3 to **4**, a 77% yield of pure **5** was obtained. When a 7:1:1 molar ratio of K_2CO_3 to Cs_2CO_3 to **4** was heated in boiling DME for 30 h, only a 70% yield of pure **5** was isolated.

Systematic Study of the Reaction 4 → 5. The data for the reactions summarized in Tables I and II were obtained under the following standard conditions: 0.16 g (0.5 mmol) of the dibenzoate **4** in 5.0 ml of the indicated solvent was heated under reflux with magnetic stirring with the indicated amount of alkali carbonate or bicarbonate for exactly 24 h. The apparatus consisted of a 10-ml round-bottom flask fitted with a reflux condenser and $CaCl_2$ drying tube attached by heavy rubber tubing to a 25-ml pipet immersed in a water-filled 500-ml graduate. Heating was accomplished by means of a magnetically stirred oil bath kept in the appropriate temperature range (73–75 °C for THF and 93–96 °C for DME), and attachment of the reaction system to the gas-measuring pipet was not made until reflux equilibrium was established (5–10 min after immersion of the reaction vessel in the preheated oil bath). In several experiments it was established that 0.5 mmol of an alkali carbonate or bicarbonate on treatment with excess acid produced an average of 13.5 ± 0.5 ml of CO_2 under the above reaction conditions. The percent yields of CO_2 listed in the table are based on this experimental volume and not on a corrected one.

At the end of the 24-h reaction time, solvent was blown off under a stream of N_2 and the cooled residue was treated with ice and excess 6 N HCl. Insoluble material was taken up in 5 ml of CH_2Cl_2 (ether, when $C_6H_5CH_2N^+(C_2H_5)_3 \cdot Cl^-$ was used as an additive) and separated. The organic layer was washed with 2 N $KHCO_3$ (2 × 4 ml) and water (3 × 4 ml), and concentrated to dryness in a warm water bath under a stream of N_2. (All separations and liquid transfers were carried out using disposable capillary pipets.) The residue was dried overnight at 60 °C in vacuo before weighing and submitting for NMR analysis. The relative amounts of **4** and **5** in the product could be determined within ±5% by virtue of the fact that, whereas **5** absorbs in the aromatic region between 6.3 and 6.9 ppm, **4** shows nothing below 7.0 ppm. Furthermore, the upfield resonance in **5** (i.e., 6.3–6.9 ppm) exhibits baseline separation from the rest of its aromatic resonance further downfield, and constitutes 29% of the total. This value was taken as the standard for pure **5**.

Acknowledgments. The author is indebted to Dr. R. Egan, Ms. R. Stanaszek, and Mr. M. Cirovic for the ^{13}C and ^1H NMR spectra, to Ms. J. Hood for the elemental analysis, and to Professor Peter Beak, University of Illinois, for helpful discussions.

Registry No.—**1**, 59873-09-5; **2**, 59873-29-9; **3**, 59873-11-9; **4**, 94-01-9; **5**, 136-36-7; $KHCO_3$, 298-14-6; K_2CO_3, 584-08-7; $CsHCO_3$, 15519-28-5; Cs_2CO_3, 534-17-8; 3-FPB, 24484-55-7.

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The Use of 1,3-Dithiane in a Regioselective Synthesis of a Novel 2-Alkyl-2-deoxy-D-arabinofuranose Branched-Chain Sugar

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Reactions of 1,3-dithiane with methyl 2,3-anhydro-5-*O*-trityl-α-D-ribofuranoside (**1a**) and methyl 2,3-anhydro-5-*O*-benzyl-α-D-ribofuranoside (**1b**) have been found to proceed in high yield and with completely regioselective nucleophilic attack at C_2. In the presence of sponge nickel catalyst, the dithiane adducts of **1a** and **1b** undergo facile dethiation to 2-deoxy-2-methyl-D-arabinofuranose sugars which are examples of a rare variety of fraudulent branched-chain sugars not readily available by chemical synthesis until now. In connection with this work a convenient new synthesis of **1b** was also developed.

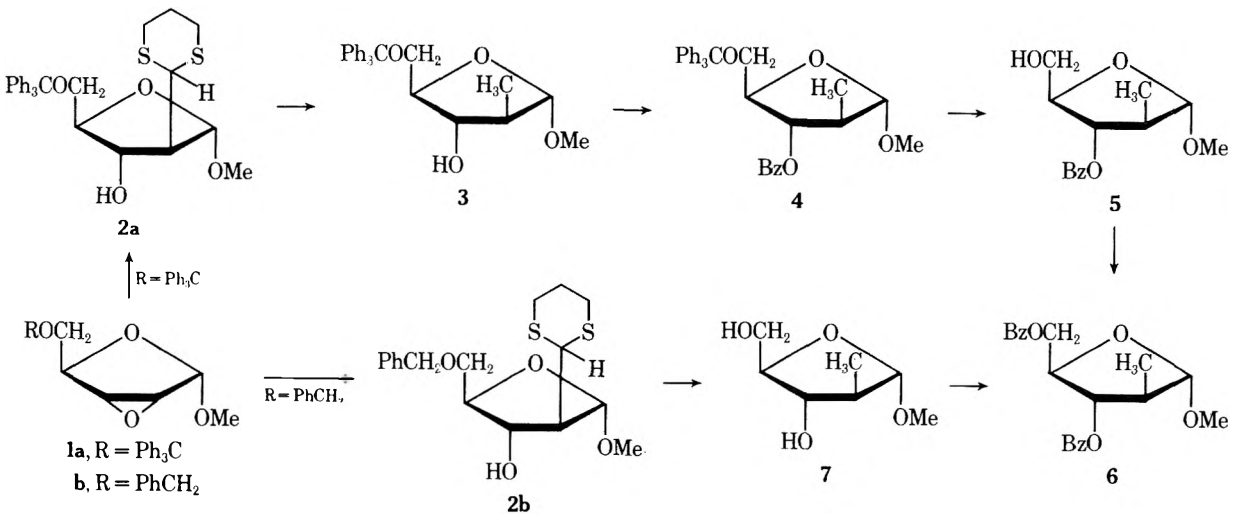
2-Alkyl-2-deoxypentofuranoses are a rare variety of fraudulent sugars which are of greatest synthetic interest as potential intermediates in nucleoside chemistry.[1,2] In this paper we wish to report the preparation of several heretofore unknown 2-deoxy-2-methyl-D-arabinofuranose derivatives by a method which takes advantage of the unexpected discovery that 1,3-dithiane adds to the epoxide ring in methyl 2,3-anhydro-5-*O*-trityl-α-D-ribofuranoside (**1a**)[3] and methyl 2,3-anhydro-5-*O*-benzyl-α-D-ribofuranoside (**1b**)[4] with completely regioselective attack at C_2, as shown in Scheme I. These results contrast sharply with the behavior of alkylmagnesium halides, which are known to give low yields and difficultly separable mixtures of 3-alkyl-3-deoxy and 2-alkyl-2-deoxy adducts on reaction with these 2,3-anhydro sugars.[5,6] The use of 1,3-dithiane offers a further advantage in that halohydrin by-products, a very significant source of difficulty in this and other Grignard reactions with epoxides,[7] cannot form. A number of papers describing the use of 1,3-dithiane with sugar epoxides[8] and ketones[9,10] have appeared in recent years, but this is the first instance in which this versatile reagent[11] has been employed successfully to cleave the epoxide ring in 2,3-anhydroribofuranose derivatives.

Addition of the 5-*O*-trityl derivative **1a** in tetrahydrofuran to a solution of 1,3-dithian-2-yllithium in tetrahydrofuran at −30 to −20 °C, followed by stirring at 0 °C for 4 days under a nitrogen atmosphere, produced an 86% yield of the adduct **2a** after column chromatography on silica gel. The presence of the dithianyl moiety in **2a** was evident from the NMR spectrum, which contained new signals at τ 7.8–8.2 and 7.0–7.4 characteristic of the $-S(CH_2)_3S-$ protons and a peak at τ 6.1 corresponding to the lone –SCHS– proton. The coupling constant of 1.5 Hz for the anomeric proton signal at τ 4.98 was consistent with trans stereochemistry for the C_1 and C_2 protons.

On being heated in the presence of sponge nickel catalyst, compound **2a** underwent dethiation to the 2-deoxy-2-methyl derivative **3** in 95% yield. The structure of **3** was apparent from its lack of identity with a sample of methyl 3-deoxy-3-methyl-5-*O*-trityl-α-D-xylofuranoside prepared for comparison via the method of Jenkins and Walton.[5] The NMR spectrum of **3** showed the expected C_2-Me signal at τ 9.0 (d, J = 7.5 Hz), and in addition revealed an upfield shift of the C_1-H signal to τ 5.42 (d, J = 1.5 Hz) which was consistent with loss of the dithianyl moiety. The deshielding effect of the dithianyl group on C_1 H was in agreement with results found by Sepulchre and co-workers[8] in the pyranose series, though the size of the shift was smaller in the furanose derivatives. Thus, **3** had to be a 2-deoxy-2-methyl derivative, and was in fact the same as the compound that Jenkins and Walton[5] had isolated but not fully characterized in their work on the reaction of methylmagnesium chloride with **1a**.

Esterification of **3** with benzoyl chloride in pyridine afforded **4** (97% yield), and removal of the 5-*O*-trityl group from **4** with acetic acid in refluxing methanol gave methyl 3-*O*-benzoyl-2-deoxy-2-methyl-α-D-arabinofuranoside (**5**, 76% yield) as an oil whose infrared spectrum contained the requisite aromatic ester peak at 1725 cm^{-1} and whose NMR spectrum showed the C_2-Me and C_1-H protons at τ 8.8 (d, J = 7.5 Hz) and 5.25 (d, J = 1.5 Hz), respectively. Esterification of **5** with benzoyl chloride in pyridine proceeded quantitatively, giving **6** as an oil with the expected infrared and NMR spectral properties. Although all the intermediates in the sequence **2a** → **6** were oils, they could be purified readily by column chromatogray on silica gel with mixtures of benzene

Scheme I



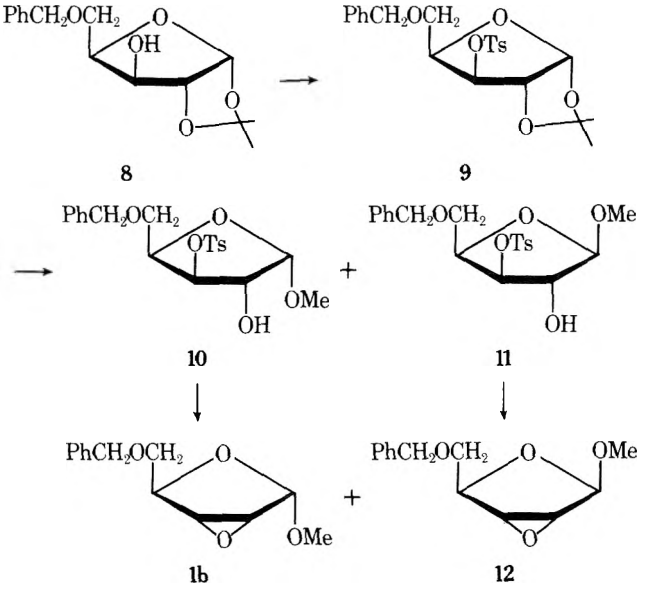
and ethyl acetate ranging in composition from 9:1 to 40:1 as eluents. The overall yield of **6** from **1a** (five steps) was 60%.

In a reaction analogous to the dithianylation of **1a**, the 5-*O*-benzyl derivative **1b** was converted to **2b** in 87% yield. The structure of **2b** was again evident from the NMR spectrum, which contained dithiane peaks at τ 7.8–8.2, 7.0–7.4, and 6.1, and a C_1-H proton signal shifted downfield to τ 4.98 (d, J = 1.5 Hz) by the neighboring dithiane moiety. Treatment of **2b** with sponge nickel in refluxing ethanol led to the desired dethiation, but also resulted conveniently in cleavage of the 5-*O*-benzyl group to give methyl 2-deoxy-2-methyl-α-D-arabinofuranoside (**7**) in 77% yield. The absence of a 5-*O*-benzyl group in **7** was apparent from its thin layer chromatographic behavior (development required pure ethyl acetate rather than benzene–ethyl acetate mixtures, and spots had to be visualized by exposure to iodine vapor since they could not be detected under ultraviolet light), and by the NMR spectrum, which contained the expected C_2-Me and C_1-H signals at τ 8.9 (d, J = 7.5 Hz) and 5.38 (d, J = 1.5 Hz), respectively, but showed no aromatic proton absorption. Diesterification of **7** with benzoyl chloride in pyridine gave a 96% yield of **6** which was indistinguishable from the material prepared via the 5-*O*-trityl epoxide **1a**. The overall yield of **6** starting from **1b** (three steps) was 64%.

Although epoxide **1b** is a known compound,[4] the method of its synthesis deserves some discussion. Wright and coworkers[4] prepared **1b** by 5-O-alkylation of methyl 2,3-anhydro-α-D-ribofuranoside with benzyl bromide and silver oxide in *N,N*-dimethylformamide. They obtained the starting epoxide via the classical six-step route of Anderson and coworkers,[12] which begins with 1,2-*O*-isopropylidene-D-xylofuranose and involves separation of the α- and β-anomeric products formed in the last step by fractional vacuum distillation.

We developed an alternative procedure for the synthesis of **1b** which is shorter by one step and avoids the need for fractional distillation. The latter point was especially advantageous for work on a preparative scale because we had previously witnessed considerable decomposition of the high-boiling α anomer when large batches of the mixed α- and β-anomeric epoxides were subjected to vacuum distillation. The synthesis of compound **1b** via this alternative route is shown in Scheme II. 1,2-*O*-Isopropylidene-D-xylofuranose was 5-*O*-tosylated and the tosyl derivative allowed to react with sodium benzylate in hot benzyl alcohol as described by Kuzuhara and Emoto[13] in order to obtain 5-*O*-benzyl-1,2-*O*-isopropylidene-D-xylofuranose (**8**), the starting point in Scheme II. The 3-hydroxy group in **8** was tosylated, the resultant product (**9**) subjected to acid-catalyzed methanolysis, and the mixture of α- and β-anomeric derivatives **10** and **11** treated with sodium methoxide to effect closure of the epoxide ring. Following separation of the anomeric products **1b** and **12** by column chromatography on silica gel, the yield of pure **1b** starting from compound **8** was 18%. This was significantly more than one can expect to obtain via the earlier route,[4] and there were fewer steps.

Scheme II



It is of interest to note that Anderson and co-workers[12] obtained a mixture of α- and β-anomeric products when they subjected 1,2-*O*-isopropylidene-5-*O*-methoxycarbonyl-D-xylofuranose to acetolysis followed by methanolysis, but the preponderant product had the β-anomeric configuration. This could be attributed to anchimeric assistance by the 2-acetoxy substituent, and Montgomery and Clayton[14] have in fact taken advantage of this phenomenon in developing a modified procedure which yields a β anomer exclusively. Whereas the use of a 5-*O*-methoxycarbonyl blocking group necessitates a separate acetolysis step prior to methanolysis (in order to achieve selective removal of the 1,2-*O*-isopropylidene group under mild conditions that leave the 5-*O*-methoxycarbonyl group intact),[12] the 5-*O*-benzyl derivative **8** can be methanolyzed *directly* because the 5-*O*-benzyl group is not affected by boiling 1% methanolic HCl. The stereochemical consequence of going from the 5-*O*-methoxycarbonyl to the 5-*O*-benzyl series is thus a significant one, in that the α/β anomeric ratio in the methanolysis step is no longer under the influence of a 2-acetoxy neighboring group.

The regioselectivity of 1,3-dithiane addition to epoxides **1a** and **1b** was not predictable a priori, and in fact we had expected by analogy with reactions of Grignard reagents[5,6] and other nucleophiles[3,12,15–17] with these epoxides that addition might take place partly, if not mainly, at C_3. The surprising lack of C_3 attack in both **1a** and **1b** is probably due to a steric effect, since the bulky dithiane molecule must approach the furanose ring from the β side where it encounters interference from the 5-*O*-trityl and 5-*O*-benzyl groups, respectively.

In summary, the work reported here offers further evidence of the usefulness of 1,3-dithiane as a synthetic reagent in sugar chemistry. The regioselectivity of attack at C_2 of the ribofuranose ring can be exploited in a number of ways. These might include, for example, the use of 2-substituted 1,3-dithianes or the conversion of the dithianyl moiety in the sugar adducts to a formyl group, which could then be elaborated into a variety of other side chain functionalities.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 137B double beam recording spectrophotometer, and NMR spectra were determined by means of a Varian T-60A instrument, tetramethylsilane being used as a reference standard. Thin layer chromatography was performed on 250-μ Analtech silica gel GF glass plates which were dried in an oven for 30 min prior to use. Spots were visualized under 254-nm ultraviolet light. Column chromatography was carried out on Baker 5-3405 silica gel (60–200 mesh). 1,3-Dithiane was obtained from Aldrich Chemical Co., Milwaukee, Wis., and 1,2-*O*-isopropylidene-D-xylofuranose was from Pfanstiehl Laboratories, Inc., Waukegan, Ill. Davison sponge nickel, the use of which in dethiation has been described previously in detail,[18] was obtained as a slurry in water from Monsanto Chemical Co., St. Louis, Mo., and was washed with ethanol prior to use. Microchemical analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Methyl 2-Deoxy-2-(1′,3′-dithian-2′-yl)-5-*O*-trityl-α-D-arabinofuranoside (2a). *n*-Butyllithium (17.8 ml of 2.3 M solution in hexane, 0.04 mol) was added with stirring, under a nitrogen atmosphere, to a solution of 1,3-dithiane (4.8 g, 0.04 mol) in dry tetrahydrofuran (50 ml) at −40 °C (bath temperature), and stirring was continued at −30 to −20 °C for 2.5 h. A solution of epoxide **1a** (1.94 g, 0.005 mol) in dry tetrahydrofuran (50 ml) was added dropwise with

continued cooling (−40 °C) and after 2 h at −30 to −20 °C the mixture was left to stir at 0 °C under nitrogen for 4 days, at which time TLC analysis showed complete absence of starting material. The reaction mixture was poured into ice water (200 ml), the product was extracted with ether (4 × 75 ml), and the combined ether extracts were washed with saturated sodium chloride (2 × 75 ml), dried over anhydrous magnesium sulfate, and evaporated. Chromatography of the oily residue on silica gel with 19:1 benzene–ethyl acetate gave an oily solid (2.1 g, 86%): ir (KCl) ν 3450 cm^{-1} (OH); NMR ($CDCl_3$) τ 7.8–8.2 (m, SCH_2CH_2), 7.0–7.4 (m, SCH_2CH_2), 6.6 (s, MeO), 6.4–6.6 (m, C_5 H), 6.1 (s, SCHS), 5.8–6.0 (m, C_2 H, C_3 H, and C_4 H), 4.98 (d, J = 1.5 Hz, C_1 H), 2.2–3.0 (m, aromatic protons).

Anal. Calcd for $C_{29}H_{32}O_4S_2$: C, 68.47; H, 6.34. Found: C, 68.46; H, 6.28.

Methyl 2-Deoxy-2-methyl-5-*O*-trityl-α-D-arabinofuranoside (3). A mixture of compound **2a** (1.6 g, 0.0032 mol) and Davison sponge nickel (45 g)[18] in absolute ethanol (450 ml) was stirred under reflux for 4 h, cooled to room temperature, and filtered. The filter cake was washed repeatedly with ethanol, and the combined filtrate and wash solutions were evaporated unde reduced pressure. The residue was dissolved in chloroform (300 ml), and a small amount of insoluble material was filtered off. Evaporation of the chloroform extract and chromatography of the oily residue on silica gel with 19:1 benzene–ethyl acetate gave compound **3** as a colorless glass (1.2 g, 95%): R_f 0.38 (9:1 benzene–ethyl acetate); NMR ($CDCl_3$) τ 9.0 (d, J = 7.5 Hz, C_2 *Me*), 7.8–8.0 (m, C_2 H), 6.4–7.0 (complex m, C_5 H), 6.6 (s, MeO), 5.8–6.1 (m, C_3 H and C_4 H), 5.42 (d, J = 1.5 Hz, C_1 H), 2.4–2.9 (m, aromatic protons).

Anal. Calcd for $C_{26}H_{28}O_4$: C, 77.20; H, 6.88. Found: C, 77.15; H, 6.88.

Methyl 3-*O*-Benzoyl-2-deoxy-2-methyl-5-*O*-trityl-α-D-arabinofuranoside (4). Compound **3** (4.1 g, 0.01 mol) was dissolved in dry pyridine (82 ml), benzoyl chloride (2.6 ml) was added dropwise with stirring, and the mixture was stirred at room temperature overnight. A few drops of water were added to dissolve the dense precipitate of pyridine hydrochloride, the solution was poured into ice water (150 ml), and the product was extracted with three portions of chloroform. The combined organic layers were washed successively with water, cold 4% hydrochloric acid, and saturated sodium bicarbonate, rinsed again with water, dried over anhydrous magnesium sulfate, and evaporated to a syrup. On removal of the last traces of pyridine via repeated azeotropic distillation with toluene, compound **4** was isolated as an amber-colored glass (5 g, 97%): R_f 0.42 (40:1 benzene–ethyl acetate); ir (thin film) ν 1725 cm^{-1} (C=O).

Anal. Calcd for $C_{33}H_{32}O_5$: C, 77.93; H, 6.34. Found: C. 77.72; H, 6.38.

Methyl 3-*O*-Benzoyl-2-deoxy-2-methyl-α-D-arabinofuranoside (5). A solution of compound **4** (5 g, 0.01 mol) in acetic acid (35 ml), water (25 ml), and methanol (20 ml) was stirred under reflux for 16 h, cooled, and evaporated to dryness under reduced pressure. After removal of all the acetic acid by repeated azeotropic distillation with methanol, the residue was chromatographed on silica gel (120 g) with 19:1 benzene–ethyl acetate as the eluent. Compound **5** was isolated as a colorless oil (2 g, 76%): R_f 0.28 (4:1 benzene–ethyl acetate); ir (thin film) ν 1725 cm^{-1} (C=O); NMR ($CDCl_3$) τ 8.8 (d, J = 7.5 Hz, C_2 Me), 7.3–7.7 (m, C_2 H), 6.6 (s, MeO), 5.9–6.1 (broad s, C_5 H), 5.5–5.9 (m, C_4 H), 5.25 (d, J = 1.5 Hz, C_1 H), 4.9–5.1 (m, C_3 H), 1.8–2.7 (complex m, aromatic protons).

Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 63.33; H, 6.96.

Methyl 5-*O*-Benzyl-2-deoxy-2-(1′,3′-dithian-2′-yl)-α-D-arabinofuranoside (2b). Epoxide **1b** (1.2 g, 0.005 mol) was allowed to react with 1,3-dithian-2-yllithium (0.04 mol) in dry tetrahydrofuran as in the preparation of compound **2a**, except that the reaction mixture was stirred for 3 h at −30 to −20 °C and then for 3 days at 0 °C. Column chromatography on silica gel with mixtures of petroleum ether (bp 30–60 °C) and ether gave compound **2b** as a yellow oil (1.55 g, 87%): ir (thin film) ν 3500 cm^{-1} (OH); NMR ($CDCl_3$) τ 7.8–8.2 (m, SCH_2CH_2), 7.0–7.4 (m, SCH_2CH_2), 6.6 (s, MeO), 6.2–6.4 (m, C_5 H), 6.1 (s, SCHS), 5.7–5.9 (m, C_2 H, C_3 H, and C_4 H), 5.4 (s, $PhCH_2$), 4.98 (d, J = 1.5 Hz, C_1 H), 2.6 (aromatic protons).

Anal. Calcd for $C_{17}H_{24}O_4S_2$: C, 57.27; H, 6.79; S, 17.99. Found: C, 57.35; H, 6.84; S, 17.85.

Methyl 2-Deoxy-2-methyl-α-D-arabinofuranoside (7). Treatment of compound **2b** (0.7 g, 0.002 mol) directly with Davison sponge nickel in boiling ethanol for 5 h, as in the synthesis of compound **3**, gave **7** as a colorless oil (0.25 g, 77%) whose properties were consistent with simultaneous dethiation and de-O-benzylation: R_f 0.42 (ethyl acetate, spot visualized by exposure to iodine vapor); NMR ($CDCl_3$) τ 8.9 (d, J = 7.5 Hz, C_2 Me), 7.8–8.0 (broad m, C_2 H), 6.6 (s, MeO), 5.8–6.4 (broad m, C_3 H, C_4 H, and C_5 H), 5.38 (d, J = 1.5 Hz, C_1 H).

Anal. Calcd for $C_7H_{14}O_4$: C, 51.84; H, 8.70. Found: C, 51.88; H, 8.68.

Methyl 3,5-Di-*O*-benzoyl-2-deoxy-2-methyl-α-D-arabinofuranoside (6). Method A. A solution of compound **5** (2 g, 0.0075 mol) in dry pyridine (60 ml) was treated with benzoyl chloride (2 ml), the mixture was stirred at room temperature overnight and poured into ice water, and the product was extracted with several portions of chloroform and worked up as in the synthesis of compound **4**. After chromatography on silica gel (80 g) with 39:1 benzene–ethyl acetate as the eluent, compound **6** was isolated as a colorless oil (2.8 g, 100%): R_f 0.46 (19:1 benzene–ethyl acetate); ir (thin film) ν 1725 cm^{-1} (C=O); NMR ($CDCl_3$) τ 8.8 (d, J = 7.5 Hz, C_2 Me), 7.4–7.8 (m, C_2 H), 6.6 (s, *MeO*), 5.2–5.6 (complex m, C_4 H and C_5 H), 5.19 (d, J = 1.5 Hz, C_1 H), 4.9–5.1 (m, C_3 H), 1.8–2.8 (complex m, aromatic protons).

Anal. Calcd for $C_{21}H_{22}O_6$: C, 68.09; H, 5.99. Found: C, 68.01; H, 5.96).

Method B. Benzoyl chloride (1 ml) was added dropwise with stirring to a solution of diol **7** in dry pyridine (30 ml), and after overnight stirring at room temperature the mixture was worked up as in the synthesis of compound **4**. Chromatography on silica gel with 39:1 benzene–ethyl acetate as the eluent gave a colorless oil (0.5 g, 96%) whose ir and NMR spectra were indistinguishable from those of the product obtained by method A.

Methyl 2,3-Anhydro-5-*O*-benzyl-α-D-ribofuranoside (1b) and Methyl 2,3-Anhydro-5-*O*-benzyl-β-D-ribofuranoside (12). A solution of compound **8** (16.8 g, 0.06 mol)[13] and *p*-toluenesulfonyl chloride (15 g, 0.079 mol) in pyridine (102 ml) was heated at 60–70 °C for 6 h in a flask protected from moisture. The mixture was cooled and poured into ice water (500 ml), and the product was extracted with chloroform (4 × 100 ml). The combined organic layers were washed with ice-cold 1% sulfuric acid, rinsed to neutrality with water, dried over anhydrous magnesium sulfate, and evaporated to a brown syrup (20 g, 87%). A solution of this material (**9**, 50 g, 0.15 mol) in 1% methanolic hydrogen chloride (1200 ml) was refluxed for 5 h, cooled, neutralized carefully with sodium bicarbonate, filtered, and evaporated under reduced pressure. The residue was taken up in water and the solution extracted with chloroform (4 × 90 ml). The combined extracts were dried over anhydrous magnesium sulfate and evaporated to a brown syrup (44 g, 82%) consisting of a mixture of **10** and **11**. This mixture (44 g, 0.11 mol) was dissolved directly in dry methanol (67 ml), to which was then added an ice-cold solution of sodium methoxide (6.4 g, 0.12 mol) in methanol (56 mol). After 4 days in a stoppered flask at about 5 °C the mixture was treated with Celite (5 g) and filtered, the filter cake was washed with methanol, and the combined filtrate and washings were neutralized with glacial acetic acid and evaporated under reduced pressure. The residue was taken up in water and the solution extracted with chloroform (4 × 90 ml). The combined extracts were dried over magnesium sulfate and evaporated, and the residue was chromatographed on a silica gel column with mixtures of petroleum ether (bp 30–60 °C) and ether ranging in composition from 9:1 to 8:2. The separation of compounds **1b** and **12** was monitored by thin layer chromatography on silica gel, with 19:6 petroleum ether–ether as the developing solvent. The faster moving product (10.9 g, 43%) was compound **12**:[19] R_f 0.33; NMR $CDCl_3$) τ 6.7 (s, MeO), 6.2–6.5 (complex m, C_3 H, C_4 H, and C_5 H), 5.7 (dd, C_2 H), 5.5 (d, $PhCH_2$), 5.13 (s, C_1 H), 2.7 (s, aromatic protons).

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 65.92; H, 6.86.

The slower component (6.3 g, 25%) was compound **1b**:[4] R_f 0.14; NMR ($CDCl_3$) τ 6.5 (s, MeO), 6.2–6.6 (complex m, C_3 H, C_4 H, and C_5 H), 5.6 (t, J = 3.0 Hz, C_2 H), 5.5 (s, $PhCH_2$), 4.86 (s, C_1 H), 2.7 (s, aromatic protons).

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.08; Found: C, 65.83; H, 6.79.

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Registry No.—**1a**, 40147-69-1; **1b**, 20187-72-8; **2a**, 59906-69-3; **2b**, 59906-70-6; **3**, 59906-71-7; **4**, 59906-72-8; **5**, 59906-73-9; **6**, 59906-74-0; **7**, 59906-75-1; **8**, 2592-42-9; **10**, 59906-76-2; **11**, 59906-77-3; **12**, 20535-09-5; 1,3-dithiane, 505-23-7; benzoyl chloride, 98-88-4; *p*-toluenesulfonyl chloride, 98-59-9.

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Polysaccharide Sequencing by Mass Spectrometry: Chemical Ionization Spectra of Permethyl Glycosylalditols[1]

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Chemical ionization (CI) mass spectra with isobutane and isobutane/ammonia as the reagent gases are reported for the six permethylated glucosylalditols and for two permethylated biosylalditols. Intense peaks corresponding to MH^+ or $(M + NH_4)^+$ were observed in all cases. In the isobutane CI spectra the ratio of abundances for the alditol ions that were formed by cleavage of the glycosidic bond on the alditol or glucosyl side of the glycosidic oxygen depended strongly on the position of the glycosidic linkage. When the linkage was 1→6, 1→2, 1→4, and 1→3 the ratio of intensities for the altitol$^+$ (A^+) and alditol hydrate$^+$ (AOH_2^+) ions were respectively 0.72, 0.37, 0.17, and 0.06. The fragmentation of a biosylalditol (7) was clearly consistent with the relative intensities for the A^+ and AOH_2^+ ions anticipated from the disaccharide results. The ratio of A^+ to AOH_2^+ was 0.16 for this 1→4 linked alditol.

Determination of the structure of oligosaccharides by mass spectrometry is directly analogous to the problem of sequencing polypeptides by the same technique. However, in the case of carbohydrates the details of the structure are considerably more subtle. Ideally one would like to obtain information about the molecular weight, subunit structure, and position sequence. Fortunately conventional techniques will give reliable information concerning subunit structure in unknown oligosaccharides. The information that must be obtained from the mass spectrum is thus reduced to molecular weight and structure and position sequence. Chemical ionization (CI) mass spectra of oligosaccharide peracetates using ammonia/isobutane[2] and isobutane[3] alone as reagent gases have been investigated in this regard.

The primary reagent ion in isobutane CI mass spectra is the *tert*-butyl cation ($C_4H_9^+$).[4] Proton transfer from this ion is considerably more exothermic than proton transfer from the ammonium ion or attachment of NH_4^+ to a molecule. The ammonium ion is the dominant reagent ion in ammonia/isobutane CI mass spectra.[2,5] The higher exothermicity of ionization in isobutane CI mass spectra results in extensive fragmentation of oligosaccharide peracetates so that the spectra resembled the electron ionization (EI) mass spectra of these molecules in many details.[3] In particular the intensity of ions with masses near the molecular weight of the molecule were quite low in both EI and isobutane CI mass spectra.

It has been possible to obtain sequence information from EI mass spectra of permethylated sugars.[6] The low intensity of the high mass ions is a distinct disadvantage in these cases and the high energies associated with the ionization process tend to cloud the structural information in the spectra.

Ammonia/isobutane chemical ionization mass spectra of oligosaccharide peracetates gave molecular weight and structure sequence information for di-, tri-, and tetrasaccharides.[2] The dominant fragment ions in these spectra corresponded to ammonium ion attachment to thermolysis fragments. The thermolysis fragments reliably produced information concerning the masses of the subunits and their sequence. However, it has not yet been possible to determine positions for the subunits in the chain from these spectra.

The permethyl derivatives of oligosaccharides are considerably less polar and more volatile than their acetate analogues. Thus it seemed reasonable to expect[2] that these derivatives might be used to give position sequence information in CI mass spectra. We have used the permethylated alditol derivatives because reduction of the carbonyl terminus of the oligosaccharide prior to methylation unequivocally tags the reducing end of the sugar for sequence analysis.

In this report we discuss the isobutane and ammonia/isobutane CI mass spectra of six permethylated glycosylalditols and two permethylated biosylalditols. The numerical designations, names, and molecular weights for these compounds are indicated in Table I.

Results and Discussion

Isobutane CI Spectra. The major ions in the isobutane CI mass spectra of the glucosylalditols, **1–6**, are presented in Table II. The most intense ion in every case corresponded to the protonated molecule. All six of the compounds in Table II showed very similar fragmentation patterns. Probable structures for the major ions and routes for their formation are illustrated for permethyl-2-*O*-β-D-glucopyanosyl-D-glu-

Table I. Names and Molecular Weights of Permethylated Glyosylalditols Examined in This Study

Compd	Name	Mol wt
1	2-*O*-β-D-Glucopyranosyl-D-glucitol	470
2	2-*O*-β-D-Glucopyranosyl-D-glucitol-*1-d*	471
3	3-*O*-β-D-Glucopyranosyl-D-glucitol-*1-d*	471
4	4-*O*-α-D-Glucopyranosyl-D-glucitol-*1-d*	471
5	6-*O*-β-D-Glucopyranosyl-D-glucitol	470
6	1-*O*-α-L-arabinopyranosyl-DL-xylitol	382
7	α-D-Glucopyranosyl-1→4-*O*-α-D-glucopyranosyl-1→4-*O*-D-glucitol	674
8	α-D-Glucopyranosyl-1→4-*O*-β-D-glucopyranosyl-1→1-*O*-DL-xylitol	630

citol (1) in Scheme I. In the spectrum of 1 and the rest of the glucosylalditols there are two major series of fragment ions, one derived from the glucosyl portion of the molecule—G^+, $(G - CH_3OH)^+$, $[G - (CH_3OH)_2]^+$—and the other derived from the alditol portion of the molecule—AOH_2^+, A^+, $(A - CH_3OH)^+$.

Since the glucopyranose end group was the same in all cases one would not expect the ions in the glucosyl series to carry significant information concerning the linkage position to the alditol. This is not true of the alditol ion series and indeed the relative intensities of alditol, A^+, and alditol hydrate ions, AOH_2^+, do vary strongly with the linkage position to the alditol. In the series **5, 2, 4,** and **3** in which the glycosidic linkage is 1→6, 1→2, 1→4, and 1→3 the ion intensity ratio for A^+/AOH_2^+ was respectively 0.72, 0.37, 0.17, and 0.06. Repeated measurements as well as the comparison between the spectra of **1** and **2** indicate that the reproducibility of these ratios is roughly ±15%. Since the ratios differ by roughly a factor of 2 in all cases it should be possible to reliably use the ratio of the A^+ (*m/e* 235) to AOH_2^+ (*m/e* 253) ions as an indication of the terminal linkage position in reduced and permethylated polysaccharides. The results for the 1→4 linked biosylalditol, **7**, are in complete agreement with this expectation (ratio of A^+ to AOH_2^+ 0.16).

The intensity ratio for the A^+ (*m/e* 191) and AOH_2^+ (*m/e* 209) for the 1→1 linked arabinosyl xylitol, **6**, was 0.65. This value is very to the ratio of A^+/AOH_2^+ for the terminally linked glycosyl alditol, **5** (0.72). The intensity ratio for the same ions for the xylitol containing trisaccharide, **8**, was 0.67, which further supports the utility of these ions in assignments of position sequence in premethylated alditols.

The formation of the A^+ ions in these spectra is easily understood by postulating protonation on the glycosidic oxygen followed by assisted cleavage to give the alditol cation. The ease of protonation as well as cleavage should be dependent on the linkage position in the alditol. Protonation on the glycosidic oxygen must also be responsible for the presence of the glucosyl ions G^+ and their fragments in the spectra.

The AOH_2^+ ions must arise by protonation at a site remote from the glycosidic oxygen[7,8] followed by elimination of the

Scheme I

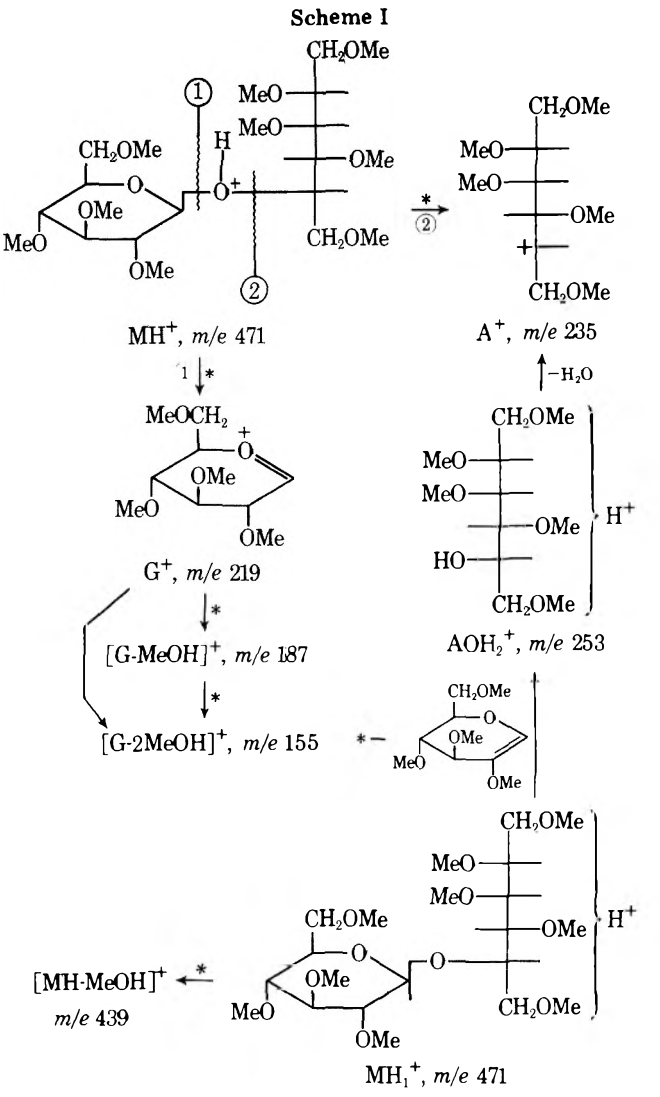


Table II. Monoisotopic Isobutane CI Mass Spectra of Permethylated Glycosylalditols[a]

Compd		MH+	MH − MeOH)+	AOH_2^+	A^+	G^+	(G − MeOH)+	(A − MeOH)+	(G − 2MeOH)+	Other ions			
1	*m/e*	471	439	253	235	219	187		155	509	194	89	
	rel intensity	100	9	25	10	1	7		10	3	2	2	
2	*m/e*	472	440	254	236	219	187		155	502	263	89	80
	rel intensity	100	20	38	13	2	13		15	2.5	4	2	4
3	*m/e*	472	440	254	236	219	187		155	509	296	113	101
	rel intensity	100	10	40	2.5	2.5	16		12	1.5	3	1.5	1.5
4	*m/e*	472	440	254	236	219	187		155	509	296	93	
	rel intensity	100	6	24	4	1	8		2.5	1.5	2	1.5	
5	*m/e*	471	439	253	235	219	187		155	509	295		
	rel intensity	100	10	3.5	2.5	0.5	3.5		3	1.0	3		
6	*m/e*	383	351	209	191	175	143	159	111	277	245	211	201
	rel intensity	100	3	13	20	9	2	1	1.5	2.5	4	1.5	5
	m/e									193	177	145	
	rel intensity									2	1.5	5	

[a] Adduct ions, e.g., $(M + C_4H_9)^+$, whose intensity strongly depends on the precise conditions in the source have not been reported. The same is true for ions with less than 1% relative abundance. [b] A = alditol moiety, G = glycosyl moiety.

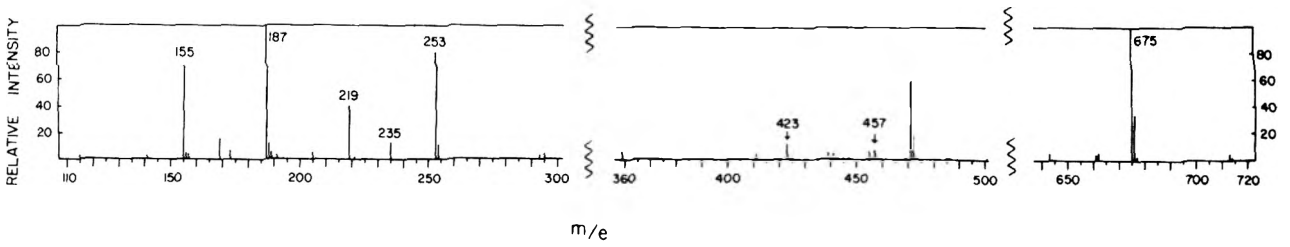


Figure 1. Isobutane CI mass spectrum of α-D-glucopyranosyl-1→4-*O*-α-D-glucopyranosyl-1→4-*O*-D-glucitol (7).

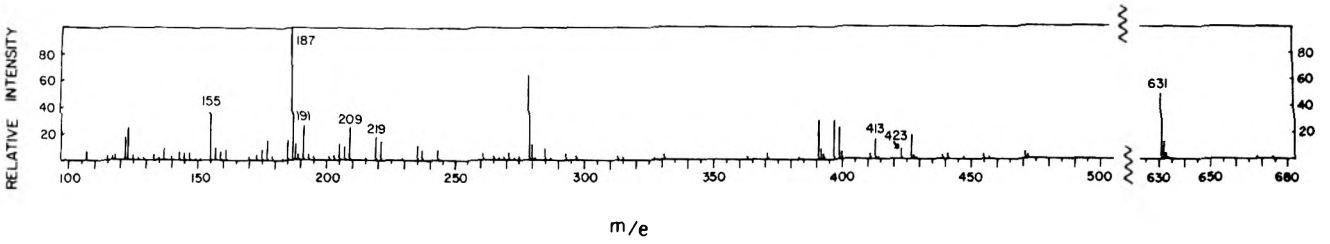


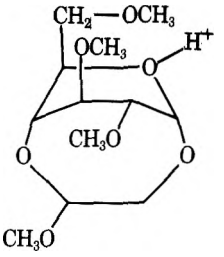
Figure 2. Isobutane CI mass spectrum of α-D-glucopyranosyl-1→4-*O*-β-D-glucopyranosyl-1→1-*O*-DL-xylitol (8).

glucosyl residue with transfer of a hydrogen atom to the alditol fragment.

The metastable ion that appeared in all of the spectra of **1–5** at *m/e* 136.2 unequivocally connects the AOH_2^+ ion with the protonated molecule. The fact that we were unable to detect a metastable ion for the reaction $AOH_2^+ \rightarrow A^+ + H_2O$ supports the contention that the precursor to the AOH_2^+ ion is not protonated on the glycosidic oxygen and thus elimination of water from AOH_2^+ would require a proton rearrangement.

The isobutane CI mass spectra of the biosylalditols **7** and **8** are illustrated in Figures 1 and 2. In both cases the protonated molecule is a prominent ion in the spectrum. The two ion types seen in the glucosylalditol spectra, namely G^+ and A^+, are the prominent fragment ion series in both of these spectra. The fragments in the G series (*m/e* 155, 187, 219, and 423) and the A series (*m/e* 235, and 457) for **7** and *m/e* 191, 209, and 413 for **8** permit unequivocal determination of the mass sequence of the residues in the chain. The origins of the G and A series ions in these spectra are indicated in Scheme II.

Other than the sequence ions, the spectra of **7** and **8** both contain a prominent ion whose origin is not obvious. The prominent ion at *m/e* 471 in the spectrum of **7** corresponds to a protonated permethyl glucosylalditol. The ammonia/isobutane mass spectrum as well as GLC analysis gave no evidence of contamination of **7** with a permethylated disaccharide and thus this ion must have arisen by methoxy or methyl transfer in cleavage of the terminal glucosyl residue. The spectrum of **8** contains a prominent ion at *m/e* 279 which does



not belong to the sequence ion series. The mass and isotope ratio suggested a formula for this ion of $C_{12}H_{23}O_7$ which would be compatible with a bicyclic structure involving the central glycosyl unit. Again the ammonia/isobutane spectra and GLC both indicated that the *m/e* 279 ion was not an artifact.

Ammonia/Isobutane CI Mass Spectra. The ammonia/isobutane mass spectra of this series of compounds have fewer prominent ions than their isobutane analogues in agreement with our expectations. The prominent ions in the ammonia/isobutane mass spectra of **1–8** are recorded in Table III.

These spectra are generally dominated by even mass ammonium ion complexes of molecules. Thus the fragments must have arisen by pyrolytic destruction of the original sugar derivatives.

The fragments in the spectra of the biosylalditols exemplify the reactions that occur. The ion at *m/e* 472 in the mass spectrum of **7** would correspond to the ammonium ion complex of a permethyl glucosylglucopyranose. This molecule was probably formed by methyl or methoxyl transfer in the cleavage of the alditol terminus. The lower intensity of the same ion in the spectrum of **8** is consistent with structure dependence of the cleavage rate. The fact that the ion appears in both spectra indicates that it does not contain the alditol portion of the molecule. The ion at *m/e* 428 in the spectrum of **7** corresponds to $C_{18}H_{34}O_{10}$: NH_4^+ which could arise by a complex thermal fragmentation process removing Cl from the central glucosyl unit along with its attached alditol. The *m/e* 400 ion contains one less CO than that at 428, and could be a product of a similar fragmentation.

Proton transfer fragment ions also appear in the spectra as indicated in Table III; however, the intensity of these ions as

Scheme II

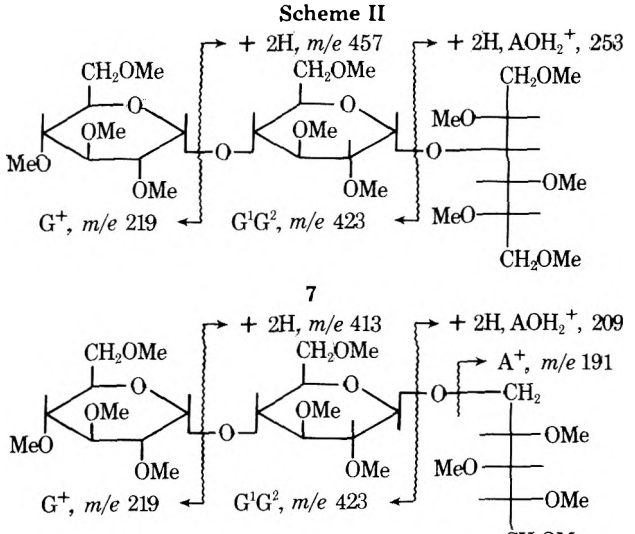


Table III. Monoisotopic Ammonia/Isobutane CI Mass Spectra of Permethylated Reduced Di- and Trisaccharides[a]

Compd		$(M + NH_4)^+$	MH^+	$(AOH + 2NH_4)^+$	AOH_2^+	A^+	Other ions				
1	*m/e*	488		270	253	235	450	439			
	rel intensity	100		4	2.5	8	5.5	3			
2	*m/e*	489	472	271		236	280	155			
	rel intensity	100	1	2		2.5	2.5	1			
3	*m/e*	489	472	271	254	236	296	210			
	rel intensity %	100	4.5	9.5			1.5	5.5	4	5	
4	*m/e*	489	472		254	236	110				
	rel intensity	100	3		1	2	2				
5	*m/e*	488	471	270	253	235	110	156			
	rel intensity	100	1.5	4.5	1	1	15	8			
6	*m/e*	400	383		191	236					
	rel intensity	100	2		1.5	5					
7	*m/e*	692					488	486	472	428	400
	rel intensity	100					12	14	25	20	8
8	*m/e*	648					414	408	302	296	157
	rel intensity	100					16	4.5	3.5	11	5

[a] Only the six most intense ions have been reported. The spectra were recorded with relatively low concentrations of the substrate in the source so that $(2M + NH_4)^+$ ions were insignificant.

well as that of the thermal fragment ions was low and generally of less structural utility than the corresponding ions in the isobutane spectra.

Summary. Isobutane CI mass spectra of permethylated saccharide alditols offer considerable promise for obtaining detailed oligosaccharide sequence information. Molecular weights and the mass sequence of monosaccharide units may be obtained directly from the spectra. The linkage position to a glucitol terminus may be inferred by the intensity ratios of alditol and alditol hydrate ions. On this basis the prospects for obtaining other position sequence information by examination of these spectra seems good.

Experimental Section

The permethylated oligosaccharide alditols used in this study were prepared by standard methods.[9] The deuterium labeled derivatives were prepared by $NaBD_4$ reduction of the parent oligosaccharide. Mass spectra were obtained by use of a solid probe inlet with an AEI MS-902 mass spectrometer equipped with an SRIC chemical ionization source. Spectra were recorded at a source pressure of 0.5 Torr (160 Pa). The source temperature was 150 °C. Ammonia/isobutane spectra were obtained with a 2:1 mixture of ammonia and isobutane at a total pressure of 0.5 Torr.

When isobutane was used as the reagent gas the intensity of the *tert*-butyl cation (*m/e* 57) exceeded the intensity of the most intense ion in the rest of the spectrum by at least a factor of 10. The recorded spectra were all obtained with the ^{13}C ion to *m/e* 58 off scale on the least sensitive range.

In the ammonia/isobutane spectra the ammonium ion (*m/e* 18) was always at least 10 times the intensity of any of the other ions in the spectrum.

Registry No.—**1**, 30608-25-4; **2**, 30608-28-7; **3**, 59907-27-6; **4**, 30608-29-8; **5**, 29923-20-4; **6**, 59907-28-7; **7**, 32581-17-2; **8**, 59907-29-8.

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(Z)-17(20)-Dehydrocholesterol. A New Sterol with C-21 and C-22 Spatially Fixed

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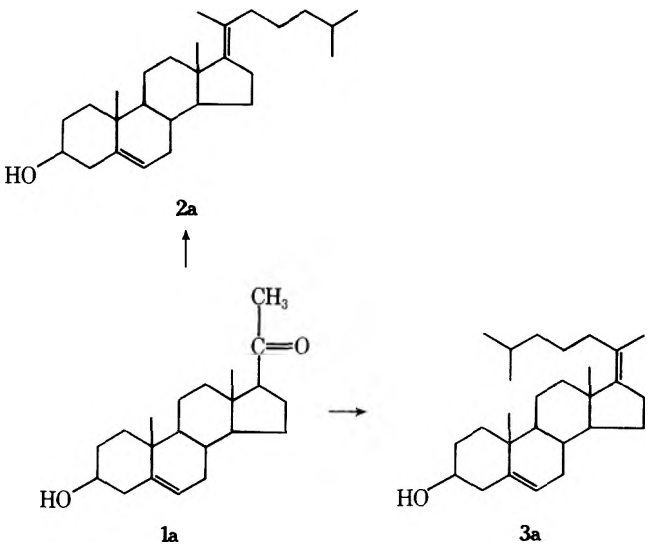
(Z)-3β-Hydroxycholesta-5,17(20)-diene, in which the side chain lies on the same side of the 17(20) bond as the sterol nucleus (C-22 cis oriented with respect to C-13), was prepared by two independent routes from pregnenolone. In one case the compound arose directly along with the previously described E isomer and E-$\Delta^{20(22)}$ analogue by the acid-catalyzed dehydration of the Grignard addition products, 20α- and 20β-hydroxycholesterol. The product composition was the same when either of the latter epimers was used and is consistent with a reaction path through an equilibrium mixture of rotationally isomeric carbonium ions bearing a positive charge on C-20 with C-22 toward or away from C-13. In the second route the cyanohydrin of pregnenolone was dehydrated with $POCl_3$ in pyridine. The (E)-$\Delta^{5,17(20)}$-nitrile produced was equilibrated in base to give the thermodynamically more stable Z isomer with the nitrile group toward C-13. After Grignard addition, reduction, and removal of the resultant 22-hydroxyl group, the title sterol was obtained. The presence and geometry of the $\Delta^{17(20)}$ bond were demonstrated by proton magnetic resonance and mass spectrometry and by conversion of the diene, through addition of osmium tetroxide followed by reduction, to the known 3β,17α,20α-trihydroxycholest-5-ene, as well as to 3β,20α-dihydroxycholest-5-ene by hydroboration. The physical and chemical evidence indicates that sterols with the natural configuration at C-20 assume a preferential conformation about the 17(20) bond such that C-21 and C-22 lie pseudoequatorially to the rear of the 17(20) bond with the third substituent on C-20 pseudoaxially oriented to the front opposing C-18.

$\Delta^{17(20)}$-Sterols are of interest owing to the fact that the side chain is fixed in space about the 17(20) bond and can be used to study the effect of spatial orientation on biological behavior, e.g., the ability to support the correct architectural characteristics of membranes or to fit into the active sites of enzymes. Furthermore, $\Delta^{17(20)}$-sterols occur naturally,[1,2] and a knowledge of their stereochemistry is of significance in understanding the mechanism of cyclization of squalene oxide.[2] In previous work[3] by one of our groups pregnenolone (**1a**) led to the $\Delta^{17(20)}$ derivative (**2a**) of cholesterol in which the side chain lies to the right (E) (Scheme I). More recently one of us

Scheme I

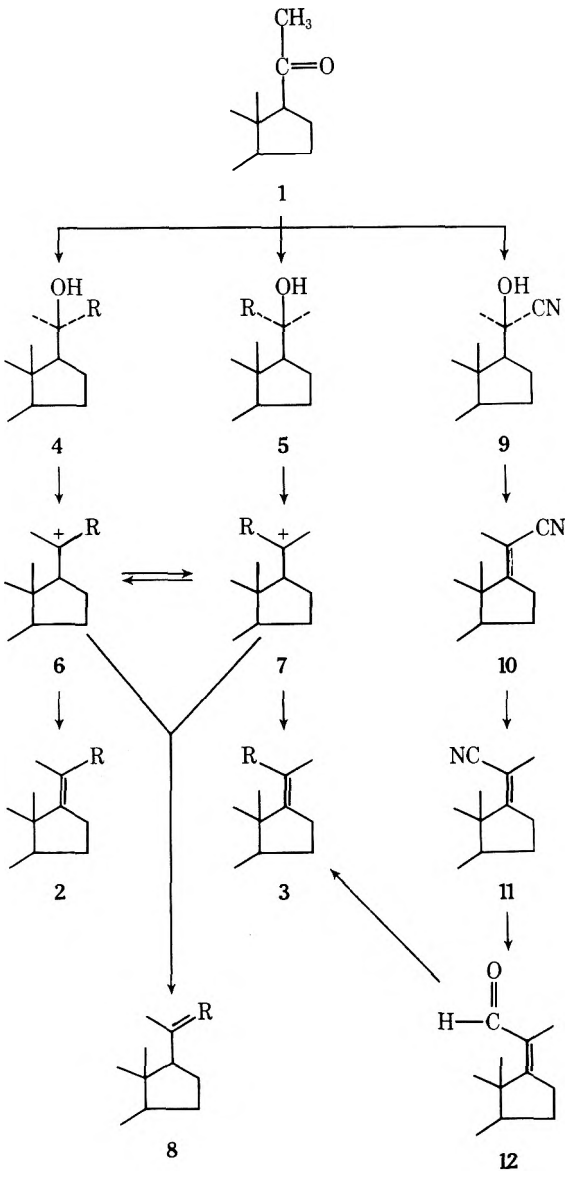


discovered a new route from pregnenolone to the E isomer, and both of us independently obtained the Z isomer (**3a**) from the same starting material but by different routes. Upon realization of this overlap, we decided to publish the work jointly. In the meantime a third route (by remote oxidation and double bond migration) to Z-$\Delta^{17(20)}$ steroids has appeared.[4] It differs among other ways from those reported here in that use of a 3β-hydroxy steroid as starting material necessarily requires inversion at C-3. In addition to obtaining the (Z)-3β-hydroxy-$\Delta^{5,17(20)}$-sterol (**3a**) and proving its structure by physical and chemical means, we have been able to shed further light on the question of rotation about a single bond between C-17 and C-20.

The most direct route (Scheme II) to the $\Delta^{17(20)}$-sterols entailed acid-catalyzed dehydration of the epimeric mixture of 20-hydroxycholesterols (**4** and **5**) derived from Grignard addition of the isohexyl group to pregnenolone (**1**, 3β-hydroxypregn-5-en-20-one). This yielded a ternary mixture in high yield of the Z and E isomers of 17(20)-dehydrocholesterol (**3** and **2**, respectively) and their E-$\Delta^{20(22)}$ analogue[5] (**8**). Each moved differently in gas–liquid chromatography, and each was obtained pure by preparative adsorption chromatography. The (Z)-$\Delta^{17(20)}$-sterol (**3**) moved faster than the other two sterols on a column of deactivated Al_2O_3, while the E isomer (**2**) was separable from the $\Delta^{20(22)}$ analogue (**8**) by argentation chromatography. Separation was also achievable on a column of lipophilic Sephadex.

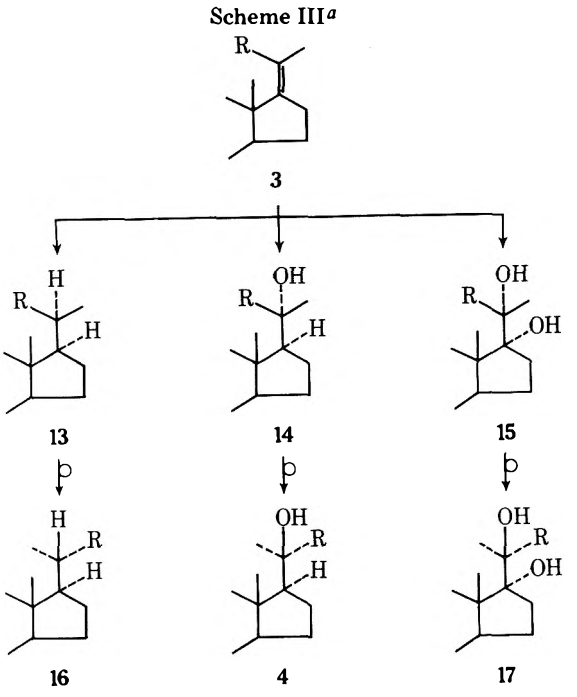
The same mixture of dienes was obtained when either 20α- (**4**) or 20β-hydroxycholesterol (**5**) was used as starting material in the dehydration. The ratio of products [(Z)-$\Delta^{17(20)}$:(E)-$\Delta^{17(20)}$:(E)-$\Delta^{20(22)}$] was 1:1:3 in both cases. Since equilibration did not occur after dehydration, the following interpretation of the mechanism is suggested (Scheme II). The proton magnetic resonance spectra of the epimeric 20-hydroxycholesterols (Table I) indicate that in their preferred conformation C-22 lies to the right in the α isomer (**4**) and to the left in the β isomer (**5**) with the 20-hydroxyl group antiparallel to the 17α hydrogen atom (opposing C-18) in both cases.[6] While such an arrangement would fulfill the requirements for a concerted elimination of water, only one of the isomeric pair of dienes (**2** and **3**) should have been obtained in each case [the Z isomer (**3**) from the β epimer (**5**) and the E isomer (**2**) from the α epimer (**4**)]. Since both isomers were obtained from each epimer, a concerted mechanism apparently does not operate. However, the alternative, a two-step process with the intermediacy of a racemized, planar carbonium ion at C-20 (**6** and **7**) fulfills the stereochemical requirements. When C-20 is in the planar state, examination of molecular models reveals little difference between the nonbonded interactions of C-21 and C-22 with

Scheme II[a]



[a] All steroids are in the Δ^5 series: R = $(CH_2)_3CH(CH_3)_2$ or $CH(CH_2)_2CH(CH_3)_2$; a, free alcohol; b, acetate; c, tetrahydropyranyl ether; d, 6β-methoxy-3,5-cyclo derivative.

Scheme III[a]



⟲ indicates rotation of 180° about the 17(20) bond

[a] Compounds 13 and 16 are 6β-methoxy-3,5-cyclo derivatives and all other steroids are in the Δ^5 series: in all cases R is $(CH_2)_3CH(CH_3)_2$; a, free alcohol; b, acetate..

the nucleus (C-12, C-18, and C-16) in the *Z* and *E* conformers. On the reasonable assumption that the tertiary carbonium ion has a half life long enough to permit rotation, approximately equal amounts of the two conformers (**6** and **7**) should exist at equilibrium which in turn would lead to approximately equal amounts of the *Z* and *E* dienes from either of the 20-hydroxy epimers (**2** from **6** and **3** from **7**) in agreement with observation.

The analysis in the preceding paragraph also leads to an explanation for the preferred conformations of the epimeric 20-hydroxycholesterols (**4** and **5**).[6] When C-20 is tetrahedral in the conformer with C-22 to the right (trans oriented to C-13), C-21 and C-22 both lie toward the rear of the 17(20) bond and therefore away from C-18 and C-16. Conversely, rotation of 180° places C-21 and C-22 in the front with substantially more interaction with C-18 and C-16. This would require, as is found, that in both epimers the 20-hydroxyl group should lie pseudoaxially in front (opposing C-18) with C-21 and C-22 pseudoequatorially to the rear.[7] As will be seen in the subsequent discussion, the same analysis explains the data known for the 17α-hydroxy derivatives of the 20-hydroxycholesterols. An important extrapolation of the argument is that cholesterol itself should also exist preferentially in the conformer with C-22 to the right (**16**, Scheme III), while in 20-isocholesterol C-22 should lie to the left.

In the second route (Scheme II) to (*Z*)-17(20)-dehydrocholesterol (**3**) the cyanohydrin (**9**) derived from pregnenolone (**1**) was dehydrated as previously described[8] to the (*E*)-$\Delta^{17(20)}$-nitrile (**10**) which in turn was isomerized to the more stable *Z* isomer (**11**). After protection of the 3β-hydroxyl group by conversion to its tetrahydropyranyl ether the cyano group was reduced with diisobutylaluminum hydride to the imine which without isolation was hydrolyzed to the aldehyde. Reaction of the latter with isopentylmagnesium bromide yielded the 22-hydroxy derivative (**12**) of (*Z*)-17(20)-dehydrocholesterol (**3**) which was isolated as its 22-methyl ether. The allylic methoxy group was reductively removed by treatment with lithium in ethylamine, and after hydrolysis of the tetrahydropyranyloxy group (*Z*)-17(20)-dehydrocholesterol (**3**) was obtained. The physical properties, including the proton magnetic resonance spectra (Table I), were identical with those of the sample derived from the first route.

The assignment of the *Z* geometry to the $\Delta^{5,17(20)}$-dienic product (**3**) follows from previous assignments of geometry to the (*E*)- and (*Z*)-$\Delta^{5,17(20)}$-nitriles.[7] Among other things which led to an assignment of structure, the protons of C-21 in the (*Z*)-$\Delta^{17(20)}$-nitrile (**11**) (bearing the C-21 methyl group away from C-13) appeared further upfield than in the *E* isomer (**10**) and no significant homoallylic coupling occurred in the *Z* isomer (**11**) with the C-16 protons as expected from other work,[9] while in the *E* isomer (**10**) the C-21 protons appeared as a triplet having J = 1.6 Hz. The same phenomenon was found with the isomeric 17(20)-dehydrocholesterols. The C-21 protons in the *Z* isomer (**3**) derived from the *Z* nitrile (**11**) appeared as an unresolved triplet at 1.55 ppm but as a distinct triplet (J = 1.7 Hz) at 1.68 ppm in the *E* isomer (**2**) derived from the *E* nitrile (**10**). The upfield shift in the signal from the C-21 protons of the *Z* isomer compared to the *E* isomer was also in agreement with expectation.[3,4,7,9]

In addition to the physical evidence chemical proof of structure was obtained (Scheme III). The (*Z*)-17(20)-dehy-

Table I. Singlet ^{1}H NMR Signals from Sterols in Parts per Million (δ)

Sterol	C-18	C-21	Origin of sterol
Cholesterol (16)	0.68		Natural product
17α-Hydroxycholesterol	0.70		From 16-dehydrocholesterol by epoxidation and reduction
17α-Hydroxycholesterol	0.70		From (Z)-17(20)-dehydrocholesterol by hydroboration
20α-Hydroxycholesterol (4)	0.87	1.28	From pregnenolone by Grignard reaction
20α-Hydroxycholesterol (4)	0.87	1.28	From (Z)-17(20)-dehydrocholesterol by hydroboration
20β-Hydroxycholesterol (5)	0.87	1.13	From 21-norcholest-5-en-3-one by Grignard reaction
17α,20α-Dihydroxycholesterol (18)	0.85	1.30	From 17α-hydroxy-21-norcholest-5-en-3-one by Grignard reaction
17α,20α-Dihydroxycholesterol (18)	0.85	1.30	From (Z)-17(20)-dehydrocholesterol by osmylation
17α,20β-Dihydroxycholesterol	0.90	1.23	From 17α-hydroxycholesterol by Grignard reaction
(E)-17(20)-Dehydrocholesterol (2)	0.86	1.68	From (E)-3β-hydroxy-20-cyanopregna-5,17(20)-diene
(E)-17(20)-Dehydrocholesterol (2)	0.86	1.68	From dehydration of 20α-hydroxycholesterol
(E)-17(20)-Dehydrocholesterol (2)	0.86	1.68	From dehydration of 20β-hydroxycholesterol
(Z)-17(20)-Dehydrocholesterol (3)	0.87	1.53	From (Z)-3β-hydroxy-20-cyanopregna-5,17(20)-diene
(Z)-17(20)-Dehydrocholesterol (3)	0.87	1.55	From dehydration of 20α-hydroxycholesterol
(Z)-17(20)-Dehydrocholesterol (3)	0.87	1.55	From dehydration of 20β-hydroxycholesterol

drocholesterol (3) was converted through the 3,5-cyclo derivative to 17α,20α-dihydroxycholesterol (15) by addition of osmium tetroxide and subsequent reductive cleavage of the Os–O bond and retro-3,5-cyclo rearrangement. Similarly, hydroboration led to 20α-hydroxycholesterol (14) (and 17α-hydroxycholesterol), and reduction of the 3,5-cyclo derivative without retro rearrangement led to 6β-methoxy-3,5-cyclo-5α-cholestane (13) which was identical with the product derived by rearrangement of cholesterol.

The proton magnetic resonance spectra (Table I) of the 20α-hydroxy- and 17α,20α-dihydroxycholesterol (4 and 17) derived from the Z-$\Delta^{5,17(20)}$-diene (3) were identical with samples prepared by the appropriate Grignard reactions with pregnenolone and with 17α-hydroxy-21-norcholest-5-en-20-one, respectively. The downfield shifts in the NMR signals (Table I) from the C-18 protons of 4 and 17 indicated that the 20-hydroxy groups were pseudoaxially in front opposing C-18 in both cases. If the 20-hydroxyl groups were not so oriented, the signal from the C-18 protons should have been near the value for cholesterol and its 17α-hydroxy derivative.[7] Since attack on the $\Delta^{17(20)}$ bond must have occurred from the rear giving 14 and 15, rotation about the 17(20) bond must have taken place afterwards leading to 4 and 17, respectively. This adds further weight to the conclusion that the most stable conformation about the 17(20) bond is the one with C-21 and C-22 pseudoequatorially oriented to the rear as shown by 4, 5, 16, and 17.

Experimental Section

General. Melting points were determined on a Kofler hot stage. NMR spectra were obtained in $CDCl_3$ at ambient temperature on a 220 or a 60 MHz instrument (Varian Associates) with an internal standard of tetramethylsilane. Chemical shifts are reported in parts per million. Mass spectra were determined on a Varian Associates M-66 spectrometer. Gas–liquid chromatography was performed in a 6-ft U-tube of 1% nitrile silicone gum (XE-60) on Chromosorb W with helium as the carrier gas at 232 °C on an F and M Model 400 instrument. Retention times are given as values relative to the retention time of cholesterol. Adsorption chromatography, unless otherwise described, was carried out on a column of alumina deactivated with 10% of water. The solvent system was ether graded into hexane. Argentation chromatography was performed with benzene graded into hexane on silicic acid impregnated with 20% of silver nitrate. Lipophilic Sephadex used for some of the separations was Lipidex-5000 supplied by Packard Instrument Co., Inc., and the solvent system was 5% hexane in methanol. The microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y. Some of the mass and NMR spectra were performed by Morgan-Schaffer Corp., Montreal 252, Quebec, Canada.

(Z)-3β-Hydroxycholesta-5,17(20)-diene (3a), (E)-3β-Hydroxycholesta-5,17(20)-diene (2a), and (E)-3β-Hydroxycholesta-5,20(22)-diene (8a) from Dehydration of 3β,20α- and 3β,20β-Dihydroxycholest-5-ene (4a and 5a). The acetate (4b) of the 20α-hydroxy steroid (4) was prepared as previously described from pregnenolone acetate (1a) by the Grignard reaction.[6,10,11] Purification was achieved by several crystallizations. While it was accompanied by the 20β epimer (5b)[6] the latter was more readily obtained pure from 3β-hydroxy-21-norcholest-5-en-20-one by Grignard addition with methylmagnesium iodide.[11] Dehydration was accomplished with 1.55 g of either of the acetates at 32 °C in 220 ml of methanol to which 4.4 ml of concentrated hydrochloric acid was added. The course of the reaction was followed by GLC, and dehydration was found to be complete during 4.0 h. Partial hydrolysis of the acetoxy group also occurred. The solvents and HCl were removed on a rotary evaporator at a temperature (ca. 50 °C) above that of the reaction which resulted in completion of the hydrolytic process. The resulting mixture showed three peaks on GLC with relative retention times of 0.88, 0.94, and 1.01 corresponding respectively to (Z)-3β-hydroxycholesta-5,17(20)-diene (3a), (E)-3β-hydroxycholesta-5,17(20)-diene (2a), and (E)-3β-hydroxycholesta-5,20(22)-diene (8a). The peaks heights were in the ratio of 1:1:3, respectively. The mixtures were essentially identical when either starting material (4a or 5a) was used, and no difference in the rates of dehydration was observed.

The (Z)-3β-hydroxycholesta-5,17(20)-diene (3a) was separated from the other two dienols by chromatography on deactivated alumina. It (3a) moved faster than the other two sterols (2a and 8a). Combination of appropriate fractions yielded 0.11 g of 3a as an oil which solidified on standing and moved in GLC with a relative retention time of 0.88. Rechromatography of fractions in which 3a was mixed with the other sterols gave an additional 0.06 g. After crystallization from acetone it (3a) melted at 119–121 °C: NMR δ 0.87 (s, 3 H, C-18), 1.02 (s, 3 H, C-19), 1.55 [s (broad), 3 H, C-21], 0.88 (d, J = 6 Hz, 6 H, C-26 and C-27); MS m/e (rel intensity) 384 (M^+, 47), 369 ($M^+ - CH_3$, 21), 351 (369 − H_2O, 24), 299 ($M^+ - C_6H_{13}$, 78), 281 (299 − H_2O, 25), 271 (299 − C_2H_4, 100), and 253 (271 − H_2O, 30). The benzoate of 3a melted at 93–94 °C: NMR δ 0.88 (s, 3 H, C-18), 1.08 (s, 3 H, C-19), 1.56 [s (broad), 3 H, C-21], and 0.88 (d, J = 6 Hz, 6 H, C-26 and C-27); MS m/e (rel intensity) 488 (M^+), 473 ($M^+ - CH_3$), 403 ($M^+ - C_6H_{13}$), 366 ($M^+ - C_6H_5COOH$, 63), 351 (366 − CH_3, 24), 281 (366 − C_6H_{13}, 100), 253 (281 − C_2H_4, 18), 228 (253 − C_2H, 17), and 212 (228 − CH_2 − 2 H, 24).

Material (0.78 g) from the alumina chromatography which moved slower than the (Z)-$\Delta^{5,17(20)}$-dienol (3a) and displayed only GLC peaks for 2a and 8a was crystallized from methanol. The precipitate (0.32 g) was composed principally of 8a. The sterol in the filtrate was acetylated (pyridine/acetic anhydride) giving 0.45 g which was chromatographed by the argentation method. The first steryl acetate to be eluted was (E)-3β-acetoxycholesta-5,17(20)-diene (2b). Combination of fractions showing a GLC peak only for 2b amounted to 0.09 g: mp 76–79 °C (methanol); NMR δ 0.86 (s, 3 H, C-18), 1.03 (s, 3 H, C-19), 1.68 (t, J = 1.7 Hz, 3 H, C-21), and 0.87 (d, J = 6, 6 H, C-26 and C-27); MS m/e (rel intensity) 366 ($M^+ - CH_3COOH$, 40), 351 (366 − CH_3, 30), 281 (366 − C_6H_{13}, 100), and 253 (281 − C_2H_4, 18). The free alcohol (2a) melted at 108–110 °C and showed a GLC peak at 0.94. The benzoate, which melted at 145–147 °C, had essentially the same mass spectrum as did the benzoate of the Z isomer except that the fragment with m/e 228 was missing. The properties of 2a and its benzoate agreed with the literature.[3]

(E)-3β-Acetoxycholesta-5,20(22)-diene (8b) appeared in fractions following those containing the (E)-$\Delta^{5,17(20)}$-dienyl acetate (2b). It (8b, 0.20 g) melted at 123–124 °C (methanol): NMR δ 0.55 (s, 3 H, C-18),

1.02 (s, 3 H, C-19), 1.63 (s, 3 H, C-21), 0.89 (d, J = 6.5 Hz, 6 H, C-26,27), 2.04 (s, 3 H, CH_3 of acetoxy group); MS m/e (rel intensity) 366 ($M^+ - CH_3COOH$, 100), 351 (366 − CH_3, 11), 281 (366 − C_6H_{13}, 4), 255 (281 − C_2H_2, 3), 254 (281 − C_2H_3, 7), 253 (281 − C_2H_4, 11), 228 (253 − C_2H, 41), 213 (228 − CH_3, 25), 211 (228 − CH_3 − 2 H, 21). The free alcohol (**8a**) melted at 136–138 °C (methanol) and showed a GLC peak with a relative retention time of 1.02: NMR δ 0.55 (s, 3 H, C-18), 1.01 (s, 3 H, C-19), 1.62 (s, 3 H, C-21), 0.88 (d, J = 6 Hz, 6 H, C-26,27). The NMR and mass spectra of the $\Delta^{5,20(22)}$-dienyl acetate (**8b**) derived from **4b** were identical with those of **8b** derived from **5b.** The properties of the (*E*)-$\Delta^{5,20(22)}$-dienol (**8a**) and its acetate (**8b**) agreed with the literature.[3,12]

When a mixture of the three dienols was chromatographed on Sephadex, **3a** was eluted first followed in order by **2a** and **8a.**

After 15 mg of (*E*)-3β-hydroxycholesta-5,20(22)-diene (**8a**) was dissolved in 10.0 ml of methanol and 0.20 ml of concentrated acid was added at 32 °C, samples were withdrawn at intervals beginning with 5.0 min and extending to 4 h. There were neither quantitative nor qualitative changes in the GLC peak, and no other peaks appeared.

(*Z*)-3β-Tetrahydropyranyloxy-20-cyanopregna-5,17(20)-diene (11c) from 10b. To a solution of 20 g of (*E*)-3β-acetoxy-20-cyanopregna-5,17(20)-diene (**10**)[8] in 250 ml of dry (freshly distilled from CaH_2) dimethyl sulfoxide 20 g of potassium *tert*-butoxide was added and the solution was stirred in a nitrogen atmosphere for 24 h. Then the solution was cooled in an ice bath and acetic acid was slowly added until the solution was neutral. After much water and ice were added the mixture was extracted with ethyl acetate and the extract was washed with water, dried with sodium sulfate, and evaporated. Thereby 12.3 g of crude **11a** was obtained which was, without further purification, dissolved in 100 ml of tetrahydrofuran containing 200 mg of *p*-toluenesulfonic acid and 8 ml of dihydropyran. This solution was kept at 20 °C for 18 h and then poured into a saturated ice-cold sodium bicarbonate solution. The product was extracted with ether, washed with water, and dried over sodium sulfate and the solvent evaporated. Purification by chromatography over Alcoa alumina gave, after recrystallization from ether, 10.30 g of pure **11c:** mp 167–171 °C; ir 2200 (conjugated–CN), 1030 and 970 cm^{-1} (ether); NMR δ 0.95 (s, 3 H, 18-CH_3), 1.33 (s, 3 H, 19-CH_3), and 1.83 (s, 3 H, 21-CH_3).

Anal. Calcd for $C_{27}H_{39}NO_2$: C, 79.17; H, 9.60. Found: C, 78.91; H, 9.45.

(*Z*)-3β-Tetrahydropyranyloxypregna-5,17(20)-diene 20-Carbaldehyde (12c) from 11c. The solution of 10.0 g of the nitrile **11c** in 400 ml of dry toluene was cooled to −70 °C, under a nitrogen atmosphere, while stirring. Then 27.0 ml of a 20% solution of diisobutylaluminum hydride in hexane was added. The solution was kept at −70 °C for an additional 30 min and then kept at room temperature overnight. Then 800 ml of a saturated ammonium chloride solution was added and the mixture was stirred vigorously for 1 h. The product was extracted with ethyl acetate, and the extract washed with water, dried, and concentrated. Purification by preparative TLC (benzene–ethyl acetate, 9:1) gave, after recrystallization from methanol, 7.0 g of pure **12c:** mp 179–181 °C; ir 1655 (–CHO), 1610 (C=C), 1030 and 960 cm^{-1} (ether); NMR δ 1.03 (s, 3 H, 18-CH_3), 1.10 (s, 3 H, 19-CH_3), 1.70 (s, 3 H, 21-CH_3), 5.35 (m, 1 H, 6-CH), and 10.27 (–CHO).

Anal. Calcd for $C_{27}H_{40}O_3$: C, 78.59; H, 9.77. Found: C, 78.43; H, 9.56.

The acetate (**12b**) was obtained in a similar manner from **11b.** A solution of 5.70 g of the *Z* nitrile (**11b**) in 200 ml of toluene was reduced with diisobutylaluminum hydride as described for its tetrahydropyranyl ether (**11c**). The residue containing the crude reduction product was acetylated and the acetate isolated in the usual fashion. The crude residue was purified by filtration of its benzene solution through a Florisil column (200 g) and the eluates were crystallized from methanol to give 3.90 g of aldehyde (**12b**): mp 140–143 °C; ir 1720 (OAc), 1635 (conjugated –CHO), and 1250 cm^{-1} (OAc); NMR δ 1.06 (s, 3 H, 18-CH_3), 1.10 (s, 3 H, 19-CH_3), 1.71 (s, 3 H, 21-CH_3, $W_{1/2}$ = 4 Hz), and 10.17 (s, 1 H, CHO).

Anal. Calcd for $C_{24}H_{34}O_3$: C, 77.80; H, 9.25. Found: C, 78.09; H, 9.18.

(*Z*)-3β-Hydroxycholesta-5,17(20)-diene (3a) from 12c. A stirred Grignard reagent solution, prepared from 1.20 g of magnesium turnings of 8.5 ml of 1-bromo-3-methylbutane in 75 ml of ether, was diluted with 50 ml of dry benzene and then the solution of 5.20 g of **3** in 50 ml of benzene was added dropwise and the solution stirred overnight. The reaction mixture was hydrolyzed with an ice-cold saturated solution of ammonium chloride. The organic material was extracted with ethyl acetate and the extract was washed with water, dried over sodium sulfate, and concentrated. The unstable crude alcohol was methylated at once by dissolving it in 25 ml of dry tetrahydrofuran and adding this solution to a solution of sodium methylsulfinylmethide in dimethyl sulfoxide (50 ml of Me_2SO and 1.0 g of NaH 50%). The solution was stirred for 3 h under nitrogen at room temperature, then 15 ml of methyl iodide was added and the solution was stirred overnight. Addition of ice and cold water followed by ether extraction gave a crude product which was purified by chromatography over 300 g of Florisil. The allylic ether was obtained pure by elution with ether–hexane (1:9) yielding 5.0 g of (*Z*)-3β-tetrahydropyranyloxy-22-methoxycholesta-5,17(20)-diene (**22**—isomeric mixture) as a mobile liquid: ir 1030 and 960 cm^{-1} (ether); NMR δ 0.83 (s, 3 H, 18-CH_3), 0.93 (s, 3 H, 19-CH_3), 0.94 (d, J = 6 Hz, 6 H, 26- and 27-CH_3), 3.17 and 3.18 (22-OCH_3) and 5.32 (m, 1 H, 6-CH).

Anal. Calcd for $C_{33}H_{54}O_3$: C, 79.46; H, 10.92. Found: C, 79.46; H, 10.86.

To a solution of 4.9 g of the allylic ether in 100 ml of anhydrous ethylamine was added rapidly 1.4 g of lithium, cut into small pieces, and the mixture was stirred until a blue color persisted for 20 min. Then the mixture was slowly poured into a cold saturated ammonium chloride solution, the product extracted with ether, and the extract washed with water, dried over sodium sulfate, and concentrated to give 4.5 g of a gummy product. To the solution of 2.10 g of the crude $\Delta^{5,17(20)}$-dienyltetrahydropyranyl ether (**3c**) in 20 ml of a tetrahydrofuran–methanol (1:1) solution was added 5 drops of concentrated hydrochloric acid and the solution heated on a steam bath for 2 h. The 3β-hydroxy product was extracted with ether, and the extract washed with water, dried, and concentrated to give, after recrystallization from acetone, 1.30 of (*Z*)-3β-hydroxycholesta-5,17(20)-diene (**3a**): mp 120–123 °C; ir 3200 and 1050 cm^{-1} (–OH); NMR δ 0.85 (s, 3 H, 18-CH_3), 0.87 (d, J = 6 Hz, 6 H, 26,27-CH_3), 1.53 (s, 3 H, 21-CH_3), 1.57 (OH), 5.35 (m, 1 H, 6-CH).

Anal. Calcd for $C_{27}H_{44}O$: C, 84.31; H, 11.53. Found: C, 84.47; H, 11.72.

(*Z*)-3α,5-Cyclo-6β-methoxy-5α-cholest-17(20)-ene (3d) from 3a. To a solution of 800 mg of the alcohol **3a** in 10 ml of pyridine was added 600 mg of *p*-toluenesulfonyl chloride and the solution kept at room temperature overnight. Then it was poured into ice, the product was extracted with ether, and the extract was washed with ice-cold 2 N hydrochloric acid and water, dried over anhydrous sodium sulfate, and concentrated to give crude tosylate. A solution of 2.50 g of the tosylate in 50 ml of methanol and 10 ml of pyridine was heated under reflux for 3 h and then most of the solvents were removed in vacuo. The residue was diluted with water and extracted with ether, dried, and concentrated. Purification on a Florisil column (100 g) gave, with 2% ether in hexane, eluates containing 1.3 g of syrupy **3d** which failed to crystallize after 2 years standing: ir 1090 cm^{-1} (–OCH_3); NMR δ 0.88 (d, 26,27-CH_3), 0.92 (18-CH_3), 1.03 (19-CH_3), and 3.33 (–OCH_3). The corresponding acetate, (*Z*)-3α,5-cyclo-6β-acetoxy-5α-cholest-17(20)-ene, was similarly prepared from the intermediate tosylate of **3a** by heating its solution in 20 ml of acetone and 5 ml of water containing 700 mg of potassium acetate under reflux for 20 h. The solvents were removed under vacuum, the residue extracted with pentane, the solution dried and concentrated, and the crude product was purified by preparative TLC to give 400 mg of syrup which was acetylated with acetic anhydride and pyridine at room temperature for 18 h. The usual workup, followed by purification or preparative TLC, gave, after recrystallization from methanol, 517 mg of the 6-acetoxy derivative: mp 114–116 °C; ir 1720 and 1230 cm^{-1} (acetate); NMR δ 0.88 (d, J = 6 Hz, 6 H, 26,27-CH_3), 0.92 (s, 3 H, 18-CH_3), 1.01 (s, 3 H, 19-CH_3), 1.55 (s, 3 H, 21-CH_3), 2.05 (s, 3 H, Ac), and 4.54 (m, 1 H, 6-CH).

Anal. Calcd for $C_{29}H_{46}O_2$: C, 81.63; H, 10.87. Found: C, 81.72; H, 11.07.

3α,5-Cyclo-5α-cholestan-6β-yl Methyl Ether (16d) from 3d. The solution of 100 mg of the syrupy olefin **3d** in 10 ml of ethyl acetate was hydrogenated (100 mg of 10% Pd/C, H_2 at 45 psi) for 40 h. The product was purified by TLC and crystallized from methanol to give 85 mg of **16d,** mp 69–71 °C,[13] ir and NMR identical with those of an authentic sample prepared from cholesterol.

(20*S*)-20-Hydroxycholesterol (4a) from 3d. To an ice-cold solution of 250 mg of the 3,5-cyclo derivative (**3d**) in 7 ml of tetrahydrofuran was added 2.5 ml of diborane–tetrahydrofuran complex and the solution stirred for 1 h at 0 °C and for an additional 1 h at 22 °C. Then 4 ml of a 2 N sodium hydroxide solution was added dropwise, the mixture was cooled to 0 °C and 4 ml of a 30% hydrogen peroxide solution was added, while stirring, and the mixture kept at 0 °C for 1 h. The product was extracted with ethyl acetate, the extract washed with a 10% sodium bicarbonate solution and water and dried, and the solvent evaporated. To the solution of the residue in 35 ml of dimethyl sulfoxide and 5 ml of water at 0 °C was added, dropwise, 2 ml of 7% perchloric acid and then 10 ml of tetrahydrofuran was added to give

a homogenous solution. The solution was kept at room temperature for 3 days, then it was diluted with water and extracted with ethyl acetate. The product was prepurified on TLC and gave 76 mg of solids. Purification on a Celite partition column (isooctane–methanol, 1:9) gave 21 mg of (20*S*)-20-hydroxycholesterol (**4a**), mp 130–132 °C (MeOH), ir and NMR identical with those of an authentic sample (Table I). In addition there was obtained 43 mg of 17α-hydroxycholesterol, mp 175–177 °C (MeOH); the ir and NMR spectra were indistinguishable from those of an authentic sample[14] (Table I).

(20*S*)-3β,17α,20-Trihydroxycholest-5-ene (17a) from 3d. To a solution of 200 mg of the 3,5-cyclo derivative (**3d**) was added 250 mg of osmium tetroxide and the mixture was kept for 5 days in the dark. Then it was poured into a solution of 500 mg of lithium aluminum hydride in 140 ml of ether and the mixture was heated under reflux for 3 h. The excess hydride was decomposed with a saturated aqueous solution of sodium sulfate and the crude product isolated in the usual fashion. The total residue was hydrolyzed with perchloric acid in the same fashion as indicated (above) for the alcohol **4a**. The product, crystallized from methylene chloride, gave 25.0 mg with mp 160–162 °C;[15] the ir and NMR spectra were superimposable on those obtained from authentic material (Table I).

Acknowledgment. This investigation was supported by Grants AM-12172 and AM-03419 from the National Institutes of Health and GB-38612 from the National Science Foundation. The authors are grateful to Mrs. D. N. Davis for some of the NMR spectra, and some of the microanalyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N.Y.

Registry No.—**2a,** 21903-19-5; **2b,** 56312-72-2; **3a,** 41083-88-9; **3d,** 59873-54-0; **4a,** 516-72-3; **4b,** 7484-20-0; **5a,** 7484-22-2; **5b,** 7429-99-4; **8a,** 59905-87-2; **8b,** 54548-85-5; **10b,** 3092-00-0; **11b,** 5143-83-9; **11c,** 58449-04-0; **12b,** 59873-55-1; **12c,** 59873-56-2; **16d,** 2867-93-8; **17a,** 382-78-5; dihydropyran, 25512-65-6; 1-bromo-3-methylbutane, 107-82-4; (*Z*)-3β-tetrahydropyranyloxy-22(*R*)-methoxycholesta-5,17(20)-diene, 59873-57-3; (*Z*)-3β-tetrahydropyranyloxy-22(*S*)-methoxycholesta-5,17(20)-diene, 59873-58-4; (*Z*)-3α,5-cyclo-6β-acetoxy-5α-cholest-17(20)-ene, 59873-59-5.

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Approaches to Analogues of Dehydrogliotoxin. 6.[1] An Efficient Synthesis of a Gliotoxin Analogue with Anti-Reverse Transcriptase Activity[2]

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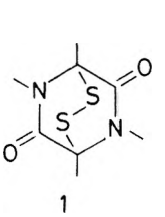
The addition of α-ketoacyl chlorides **4** to indolenine-2-carboxamides **3,** followed by spontaneous, diastereoselective ring closure to 3,6-disubstituted dioxopiperazines (**5** → **6**), provides an efficient, new synthesis of gliotoxin analogues. Compound **6** was converted into the mercaptoalkene **11** by treatment with H_2S. Regiospecific and diastereoselective addition of H_2S to the exo methylene group gave cis dithiol **12.** This zinc ion catalyzed reaction is believed to proceed via the chelate intermediate **19a.** Several oxidation procedures were studied for the conversion of **12** into disulfide **13.** The tri- and tetrasulfides **21** and **22** were obtained from **12** by reaction with SCl_2 and S_2Cl_2, respectively; the monosulfide **20** was obtained from **13** by treatment with $(C_6H_5)_3P$. Analogies between this synthesis and what is known about the biosynthesis of gliotoxin are discussed. Compound **13** thus obtained (81% overall yield) was found to inhibit the enzyme reverse transcriptase, while having no effect on transcriptase; its activity is comparable to that of gliotoxin.

The epidithiodioxopiperazine system **1,** common to a number of fungal metabolites, including dehydrogliotoxin (**2**), the sporidesmins, aranotins,[5] and others,[6] appears to be the site of the potent antiviral, antibacterial, or antifungal activities of this group of compounds. Several syntheses of simple derivatives of **1** have appeared[7] and Kishi and coworkers have recently reported a 12-step synthesis of (±)-dehydrogliotoxin (**2**).[8] We wish to report the development of



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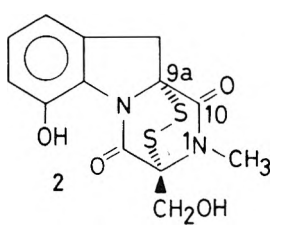

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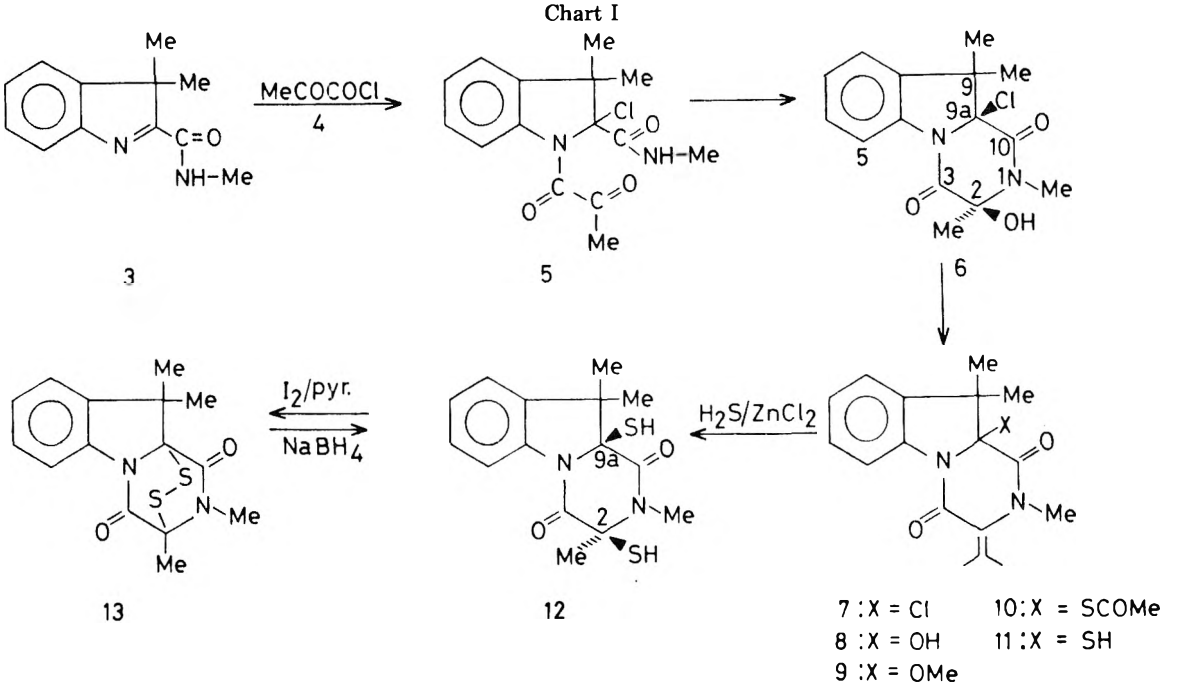
Chart I



a scheme which forms the epipolythiodioxopiperazines **13** and **20–22** in a high yield, three-step, one-pot reaction under mild conditions, and which may be of general applicability for other dehydrogliotoxin analogues.

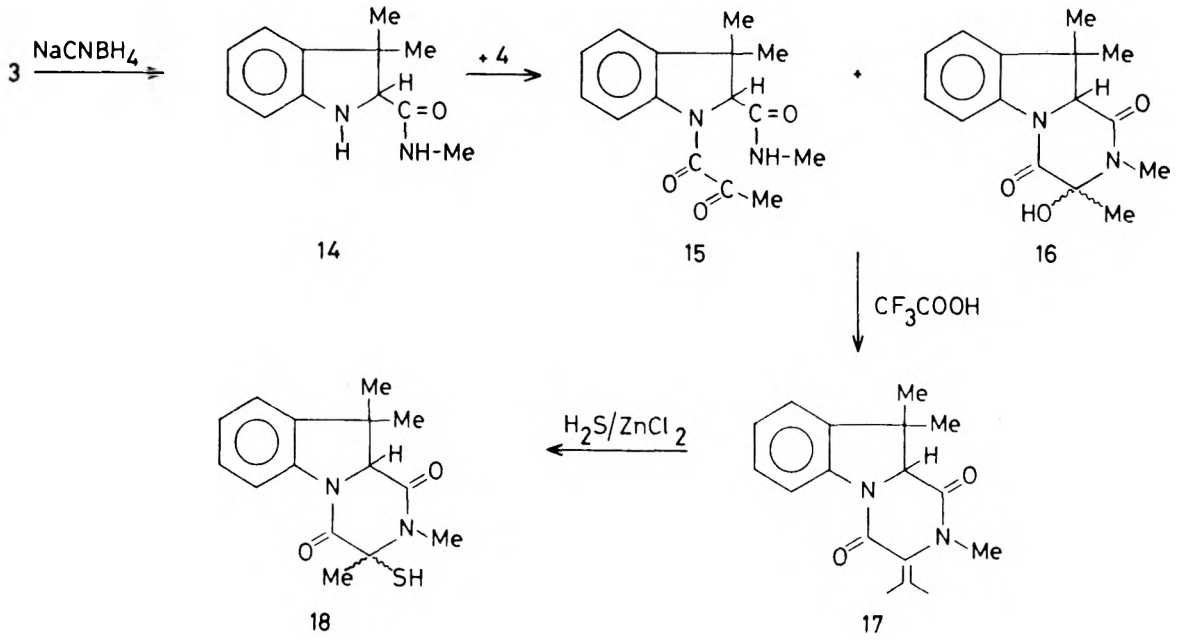
Although dehydrogliotoxin (**2**) can be viewed as an oxidized condensation product of a 2-mercaptoindoline-2-carboxylic acid and an α-mercapto-α-amino acid derivative, neither of these components is evidently capable of independent existence. We have evidence[9] that unacylated indoline-2-thiols are inherently unstable and, so far as we know, no unacylated α-mercapto-α-amino acid has yet been synthesized. Accordingly, we felt that a synthetic procedure for this system would have to create a functional group at the indoline C_2 position, convertible to a mercapto group, simultaneously with the acylation of the indoline nitrogen by an α-mercapto-α-amino acid equivalent. Our initial synthetic approach involved[9] the ring closure ($N_1 \rightarrow C_{10}$) of a *seco*-gliotoxin analogue, prepared in this manner. This reaction failed, apparently because the necessarily strenuous reaction conditions we employed were incompatible with a strained ring system. For this reason we turned to a scheme featuring a preformed dioxopiperazine ring but having groups at the α positions capable of being converted to mercapto groups. Two particular reactions, run consecutively, could, we thought, create such an intermediate (Chart I): (1) the addition (**3** → **5**) of acyl chlorides (e.g., **4**) to the imine bond of indolenines **3** and (2) the intramolecular cyclization (**5** → **6**) of an amide nitrogen with the α-carbonyl group of an α-ketoacyl residue. The former is a general reaction discovered by Leuchs,[10] later employed[11] by Wieland in the synthesis of an *N*-acylindoline 2-thioether and recently by us[9] as a convenient route to 1-acyl-2-mercaptoindoline-2-carboxylic acid esters. Reaction 2, discovered by Bergmann and Grafe,[12] who studied intermolecular reactions of primary or secondary amides with pyruvates, has been employed by us[1] as a practical route to α-mercapto-α-acylamidocarboxylic acids.

After we had developed a practical preparation of the hitherto elusive pyruvoyl chloride (**4**),[13] these two synthetic ideas were applied as follows. Pyruvoyl chloride (**4**) and the indolenine carboxamide **3** in CCl_4 reacted within 50 min at room temperature to form the Leuchs' adduct **5**. About 5 h after mixing, this intermediate was converted completely into **6** and appeared to be only one stereoisomer by ^1H NMR spectroscopy.

This diastereoselective[14] ring closure of **5**, which has been observed recently by others[15,16] in closely related systems, has been rationalized by Häusler and Schmidt[15] and is predicted to give the cis product **6**. After our work had been completed,[2] however, a report by Poisel and Schmidt[17] suggested that the reaction might not be stereoselective in all cases.

We first attempted the direct conversion of **6** to the dithiol **12** by treatment with H_2S. However, **6** was found to be unstable; when stirred for 10 h it is transformed into a mixture of **7** and **8**, the latter apparently arising from the water produced on spontaneous dehydration. The chloroalkene **7** could be converted quantitatively into **8** with 1 equiv of H_2O in pyridine, while treatment with $MeOH/CCl_4$ or thioacetic acid and BF_3-Et_2O in CH_2Cl_2 gave **9** (96%) and **10** (45%), respectively. When H_2S was bubbled through a CH_2Cl_2 solution of **6** or **7** for 1 h at room temperature, the mercaptoalkene **11** resulted. We then faced the problem of converting **11** into **12**. Recently, Machin and Sammes[18] and Marshall et al.[16b] showed that only in the presence of strong acids are sulfur nucleophiles added in α fashion across the double bond of dehydro cyclodipeptides, whereas under weakly acidic conditions β-addition is observed. When **11** is exposed to H_2S in the presence of boron trifluoride etherate or *p*-TosOH, an intractable reaction mixture resulted. When, however, the reaction of **11** is conducted in an all-glass pressure flask containing liquid H_2S at room temperature with CF_3COOH as catalyst, a 50% yield of the cis dithiol **12** resulted besides unidentifiable material. Although this avoids the time-consuming process of bubbling H_2S through a CH_2Cl_2 solution of **11** (where reaction also occurs), we felt that the general applicability of our scheme would be compromised by these acidic reaction conditions and consequently we searched for milder ones. We reasoned that H_2S might be converted into a strong enough acid to catalyze this reaction by chelation with transition metal ions; zinc chloride was chosen for the initial study[19] and was tested with the model compound **17**, which was prepared in the following manner (Chart II). Reduction of **3** with $NaCNBH_3$, followed by reaction with **4** in the presence of the Hünig base, gave a 3:1 mixture of **15** and **16**, respectively; treatment with a trace of CF_3COOH gave **17** in 83% overall yield. When alkene **17** was allowed to react with liquid H_2S in the presence of $ZnCl_2$, only one α-substituted stereoisomer **18** (unknown stereochemistry) resulted quantitatively.

Chart II



Encouraged by this result, we exposed the mercaptoalkene **11** to these conditions, and it yielded quantitatively the α adduct **12**. This reaction was also found to proceed in a diastereoselective fashion, as only the cis dithiol could be detected. The possibility that a trace of HCl, from hydrolysis of $ZnCl_2$, was the true catalyst could be excluded by the observation that dry HCl only gave an intractable reaction mixture. The zinc chloride catalyzed regiospecific and diastereoselective addition reaction could be explained in the following way. A zinc complex with the C_{9a} SH group in **11**[19] might direct the incoming SH groups from the same face by complexation (**19a**, Chart III), yielding **12**. Cis addition could also be explained if **19b** were to represent the preferred conformation of **11**. This conformer relieves the interaction of NCH_3 with an exomethylene hydrogen in **19a** but shields the α-face of the exomethylene group by the 9(α)-methyl group. Although slightly nonplanar (5–10°) amide bonds in dioxopiperazines have precedent,[20a] the significant deviation from planarity implied in **19b** may make it a less likely explanation for the observed stereochemistry.

We do have some evidence that the cis configuration of **12** may be thermodynamically more stable than the trans form, as the above-mentioned CF_3COOH-catalyzed reaction of **11** with H_2S gave *cis*-**12** (50%) besides unidentifiable products among which no trans isomer of **12** could be detected.[20b] We have no firm evidence, however, that equilibration occurs under these conditions.

The cis orientation of the C_2 and C_{9a} thiol groups in **12** is proved by its ready oxidation to the epidithiodioxopiperazine **13**. This oxidation can be performed by simply bubbling air through an aqueous methanol solution of **12** in the presence of traces of $ZnCl_2$[21] (37% overall yield from **3**). The yield could be improved slightly (51%) by using KI_3 as an oxidant in a two-phase system.[7b,22] Finally the method of choice for this oxidation was discovered to be I_2 in CH_2Cl_2 in the presence of pyridine under anhydrous conditions. This raised the overall yield of **13** to 81% after column chromatography and made the three-step route (**3** → **7** + **8** → **12** → **13**) a truly practical, one-pot synthesis.

The disulfide **13** could be reduced to the dithiol **12** (80%) by treatment with $NaBH_4$ in C_2H_5OH.[5] Reaction with $(C_6H_5)_3P$[23] in dioxane gave the strained monosulfide **20** in 93% yield (Chart IV); using methanol instead of dioxane in this

Chart III

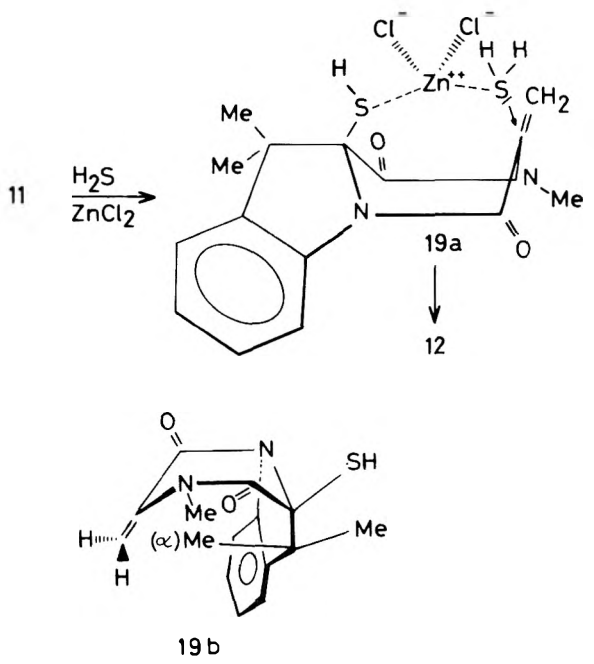
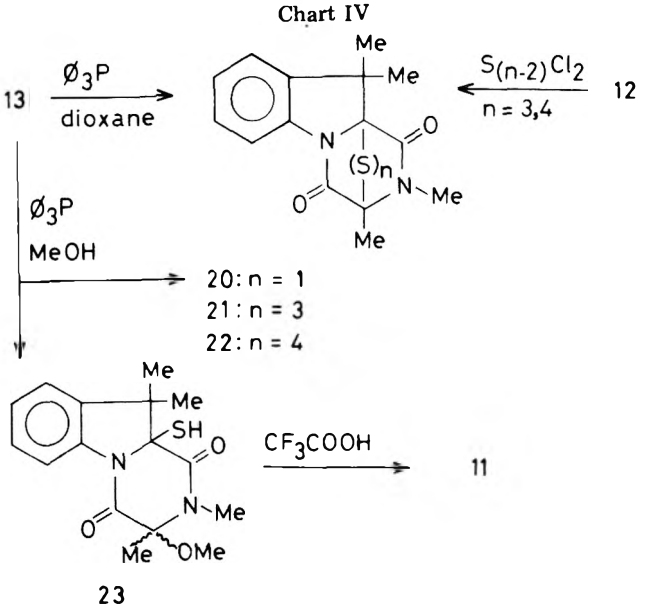
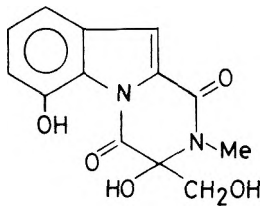


Chart IV



reaction yielded besides **20** (33%) the ring-opened **23** (63%), which could be converted into **11** by treatment with CF_3COOH. The formation of **23**[24] indicates a regioselective attack of the phosphine on the less hindered sulfur atom of **13**. The dithiol **12** could be converted into the trisulfide **21** or tetrasulfide **22** by treatment with SCl_2[25a] or S_2Cl_2,[25b] respectively. At room temperature **21** exists in two conformations, as was concluded from the ^1H NMR spectrum. A similar observation has been reported on the trisulfide sporidesmin E.[26]

The similarity of structures **6** and **7** to the metabolites **24** and **25**, which are postulated to be intermediates in the bio-



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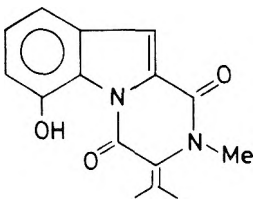

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synthesis of gliotoxin,[5] is apparent. This, together with the facts that the route **3** → **13** involves highly stereoselective, high-yield reactions and can be carried out at room temperature and neutral pH, tempts us to speculate that our sequence could be a biomimetic one.

Biological Activity. Compound **13** was found to inhibit reverse transcriptase, the RNA-dependent DNA polymerase of RNA tumor viruses. Thus, in the presence of 3.9×10^{-4} M (130 μg/ml) and 3.9×10^{-5} M (13 μg/ml) of **13**, the poly A-dependent incorporation of 3H-dTMP residues in an enzyme preparation derived from Rauscher leukemia virus was 14 and 41% of the blank activity, respectively.[27] This activity is of the same order of magnitude as that for gliotoxin. The latter inhibited endogenous reverse transcriptase activity of Rauscher sarcoma virus: with 50 μg/ml, 25% of the enzyme activity remained.[28]

Earlier we found that an analogue of **13**, having a methylene sulfide bridge, was devoid of antiviral and antibacterial activity.[29] These results again lend support to the proposal that natural products containing the epidithiodioxopiperazine moiety require the disulfide bridge for biological activity.

No activity of **13** on the transcriptase (DNA-dependent RNA polymerase) of *E. coli* bacteria was found.[30] This selectivity is of interest as another epidithiodioxopiperazine, i.e. acetylaranotin, is a highly selective inhibitor of transcriptase.[24b]

Experimental Section

Infrared spectra were measured with a Perkin-Elmer spectrophotometer, Model 257. Proton magnetic resonance spectra were measured on a Varian Associates Model A-100 spectrometer. Chemical shifts are reported as δ values (ppm) relative to hexamethyldisiloxane as an external standard; deuteriochloroform was used as solvent unless stated otherwise. Mass spectra were obtained with a double-focusing Varian Associates SMI-B spectrometer (electron impact), or a Finnigan mass spectrometer 1015D with Model 6000 data system (chemical ionization). Melting points were taken on a Köfler hot state (Leitz-Wetzlar) and are uncorrected. Thin layer chromatography (TLC) was carried out using Merck precoated silica gel 60F-254 plates, thickness 0.25 mm. Spots were visualized with a uv hand lamp, iodine vapor and, in the case of sulfur-containing products, by spraying with 2% aqueous $AgNO_3$.[24b]

***N*-Methyl-3,3-dimethylindolenine-2-carboxamide (3).** A solution of 2.17 g (10 mmol) of ethyl 3,3-dimethylindolenine-2-carboxylate[9] in 30 ml of dimethoxyethane containing methylamine (8 M) was kept at 80 °C in an autoclave for 16 h (pressure 11–12 atm). Evaporation of the solvent and excess reagent gave a crystalline mass which was recrystallized from hexane, to give **3** in 90% yield: mp 109–110 °C; ir ($CHCl_3$) 3410 (NH), 1670 (amide), and 1545 cm^{-1} (C=N); NMR (CCl_4) δ 7.87 (m, 1 H, C_7H), 7.65 (m, 3 H, C_{4-6} H), 3.28 (d, 3 H, NCH_3) and 1.80 (s, 6 H, 2 C_3CH_3). Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.97; N, 13.86. Found: C, 71.3; H, 7.0; N, 13.9.

9,9a-Dihydro-1,9,9-trimethyl-2-methylene-3,10-diketo-9a-chloropiperazino[1,2-*a*]indole (7) and 9a-Hydroxy Analogue 8. To a stirred solution of 1.01 g (5 mmol) of **3** in 25 ml of dry CCl_4 was added at room temperature 586 mg (5.5 mmol) of pyruvoyl chloride (**4**).[13] After stirring for 5 h at room temperature the ring closure product **6** had formed quantitatively, as was shown by infrared and ^1H NMR spectroscopy: ir (CCl_4) 3600–3100 (OH) and 1685 cm^{-1} (br), C=N band had disappeared; NMR (CCl_4) δ 8.32 (m, 1 H, C_5 H), 7.63 (*m*, 3 H, C_{6-8}H), 6.44 (s, br, 1 H, OH), 3.49 (s, 3 H, NMe), 2.18 (s, 6 H, C_9 $C_\alpha H_3$ and C_2 CH_3) and 1.60 (s, 3 H, C_9 $C_\beta H_3$).

After stirring for 10 h, **6** was converted completely into a mixture of **7** and **8** (varying ratios) which is poorly soluble in CCl_4. The addition of 4Å molecular sieves to a solution of **6** did not prevent the formation of **8**.

Chloroalkene **7**: ir ($CHCl_3$) 1695 cm^{-1} (amide); NMR δ 8.65 (m, 1 H, C_5 H), 7.75 (m, 3 H, C_{6-8} H), 6.54 (d, 1 H, C=CH_α), 5.66 (d, 1 H, C=CH_β), 3.76 (s, 3 H, NMe), 2.27 (s, 3 H, C_9 $C_\alpha H_3$), and 1.72 (s, 3 H, C_9 $C_\beta H_3$).

Hydroxyalkene **8**: mp 178–183 C; ir ($CHCl_3$) 3600–3100 (OH) and 1690 cm^{-1} (amide); NMR δ 8.65 (m, 1 H, C_5 H), 7.75 (m, 3 H, C_{6-8} H), 6.44 (d, 1 H, C=CH_α), 5.53 (d, 1 H, C=CH_β), 3.68 (s, 3 H, NMe), 2.13 (s, 3 H, C_9 $C_\alpha H_3$) and 1.62 (s, 3 H, C_9 $C_\beta H_3$); mass spectrum *m/e* 272 (M^-), 255 (M^+ − OH), and 240 (M^+ − OH − CH_3).

9,9a-Dihydro-1,9,9-trimethyl-2-methylene-3,10-diketo-9a-methoxypiperazino[1,2-*a*]indole (9). Excess MeOH (20 ml) was added to a stirred solution of 291 mg (1 mmol) of **7** in 5 ml of CCl_4 at oom temperature. After stirring for 1 h, solvents and excess reagent were removed in vacuo, to yield 280 mg (96%) of oily residue: NMR δ 8.24 (m, 1 H, C_5 H), 7.40 (m, 3 H, C_{6-8} H), 6.25 (d, 1 H, C=CH_α), 5.37 (d, 1 H, C=CH_β), 3.55 (s, 3 H, OMe), 3.35 (s, 3 H, NMe), 1.93 (s, 3 H, C_9 $C_\alpha H_3$) and 1.39 (s, 3 H, C_9 $C_\beta H_3$); mass spectrum *m/e* 286 (M^+), 271 (M^+ − CH_3), 255 (M^+ − OCH_3), and 240 (M^+ − CH_3 − OCH_3).

9,9a-Dihydro-1,9,9-trimethyl-2-methylene-3,10-diketo-9a-thioacetylpiperazino[1,2-*a*]indole (10). Thioacetic acid (182 mg, 2.4 mmol) and then 1 drop of BF_3·$(C_2H_5)_2O$ were added to a stirred solution of 582 mg (2 mmol) of **7** in 10 ml of dry CH_2Cl_2 at room temperature. After stirring for 3 h at room temperature, the solvent and excess reagent were removed in vacuo, to yield a crystalline mass, which was recrystallized from MeOH–hexane: mp 167–169 °C; yield 297 mg (45%); TLC (4% C_2H_5OH–toluene), only one spot; ir ($CHCl_3$) 1690 cm^{-1} (br, C=O); NMR δ 8.37 (m, 1 H, C_5 H), 7.57 (m, 3 H, C_{6-8} H), 6.38 (d, 1 H, C=CH_α), 5.45 (d, 1 H, C=CH_β), 3.68 (s, 3 H, NMe), 2.53 (s, 3 H, $SCOCH_3$), 2.09 (s, 3 H, C_9 $C_\alpha H_3$), and 1.51 (s, 3 H, C_9 $C_\beta H_3$); mass spectrum *m/e* 330 (M^+), 287 (M^+ − $COCH_3$), 273 (M^+ − MeN=C=O), and 255 (M^+ − $SCOCH_3$). Anal. Calcd for $C_{17}H_{18}N_2SO_3$: C, 61.80; H, 5.49; N, 8.48. Found: C, 62.0; H, 5.6; N, 8.5.

9,9a-Dihydro-1,9,9-trimethyl-2-methylene-3,10-diketo-9a-mercaptopiperazino[1,2-*a*]indole (11). H_2S saturated with CH_2Cl_2 was bubbled for 2 h through an ice-cooled, stirred CH_2Cl_2 solution of a mixture of **7** and **8** (1 mmol) to which was added a few crystals of anhydrous zinc chloride. The reaction mixture was filtered and the solvent evaporated in vacuo, to yield a crystalline mass, which on TLC (5% CH_3OH–$CHCl_3$) showed only one spot: ir ($CHCl_3$) 2570 (SH) and 1690 cm^{-1} (br, CO); NMR δ 8.56 (m, 1 H, C_5 H), 7.68 (m, 3 H, C_{6-8} H), 6.42 (d, 1 H, C=CH_α), 5.52 (d, 1 H, C=CH_β), 3.71 (s, 3 H, NMe), 3.10 (s, 1 H, SH), 2.18 (s, 3 H, C_9 $C_\alpha H_3$), and 1.68 (s, 3 H, C_9 $C_\beta H_3$); mass spectrum *m/e* 288 (M^+) and 255 (M^+ − SH).

9,9a-Dihydro-1,2,9,9-tetramethyl-2,9a-dimercapto-3,10-diketopiperazino[1,2-*a*]indole (12). From 7 + 8. Dried H_2S (about 10 ml) was condensed at −70 °C into a dry CH_2Cl_2 solution (75 ml) of a mixture of **7** and **8** (5 mmol), to which was added an excess (7 mmol) of anhydrous zinc chloride. The all-glass pressure flask was closed, and the reaction mixture was stirred at room temperature for 16 h, during which time the pressure increased to about 8 atm. Then the flask was opened, the reaction mixture filtered, and the solvent evaporated in vacuo, to yield a glassy material which showed on TLC (2% CH_3OH–CH_2Cl_2) besides a spot on the origin (**12**) a faint spot corresponding to **13** which indicates the easy oxidation of **12**. Formation of **13** was not observed when traces of CH_2Cl_2-soluble zinc ions were removed from the product before bringing on TLC plates: ir ($CHCl_3$) 2570 and 2540 (SH), 1685 cm^{-1} (CO); NMR δ 8.51 (*m*, 1 H, C_5 H), 7.68 (m, 3 H, C_{6-8} H), 4.27 (s, br, 1 H, SH), 3.60 (s, 3 H, NMe), 3.44 (s, 1 H, SH), 2.42 (s, 3 H, C_2 CH_3), 2.21 (s, 3 H, C_9 $C_\alpha H_3$), and 1.59 (s, 3 H, C_9 $C_\beta H_3$); mass spectrum *m/e* 322 (M^+), 289 (M^+ − SH), 288 (M^+ H_2S), 279 (M^+ − $COCH_3$), 274 (M − SH − CH_3), 273, 261, 260, 256, 255, and 241 (M^+ − SH − SH − CH_3).

From 13. To an ice-cooled stirred solution of 145 mg (0.43 mmol) of **13** in 25 ml of dry C_2H_5OH was added 57 mg (1.5 mmol) of $NaBH_4$ in one portion. After stirring for 10 min at 0 °C another 57-mg portion of $NaBH_4$ was added. Stirring was continued for 20 min at 0 °C and finally 15 min at room temperature. After evaporation of the solvent in vacuo, water and $CHCl_3$ were added and the pH adjusted at 7 with 2 N H_2SO_4. The aqueous layer was extracted twice with $CHCl_3$. The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo to give 110 mg (76%) of **12**, identical with the above specimen, except for no tendency toward oxidation on TLC.

9,9a-Dihydro-1,2,9,9-tetramethyl-2,9a-epidithio-3,10-diketopiperazino[1,2-*a*]indole (13). Oxygen Oxidation. Air was bubbled through a solution of 840 mg (2.54 mmol) of **12** (prepared from **7** + **8**) in 15 ml of 80% CH_3OH–H_2O, for 2.5 h at room temperature. Removal of the solvent and chromatography of the residue on Sephadex LH-20 in 80% CH_3OH–H_2O (column 3.4 × 167 cm, flow rate 52 ml/h, 15-ml fractions) afforded 292 mg (36%) of **13** (mp 142–144 °C recrystallized from CH_3OH–H_2O) which was homogeneous by TLC (R_f 0.50, 4% CH_3OH–toluene, R_f 0.57, 2% CH_3OH–CH_2Cl_2): ir ($CHCl_3$) 1692 cm^{-1} (CO); NMR δ 8.37 (m, 1 H, C_5 H), 7.62 (m, 3 H, C_{6-8} H), 3.47 (s, 3 H, NMe), 2.45 (s, 3 H, C_2 CH_3), 2.14 (s, 3 H, C_9 $C_\beta H_3$), and 1.95 (s, 3 H, C_9 $C_\beta H_3$); mass spectrum (electron impact, only peaks with rel intensity >20) *m/e* 320 (M^+, 39), 256 ($M^+ - S_2$, 81), and 241 ($M^+ - S_2 - CH_3$, 100); (chemical ionization, NH_3) *m/e* 338 ($M + NH_4^+$, 33), 321 ($M + H^+$, 100), and 257 ($M + H^+ - S_2$, 71).

Anal. Calcd for $C_{15}H_{16}N_2O_2S_2$: C, 56.23; H, 5.03; N, 8.74; S 20.01. Found: C, 56.0; H, 5.1; N, 8.5; S, 20.1.

Iodine Oxidation. A 2.5% solution of KI_3 in pyridine was added dropwise at room temperature to a solution of 1.61 g (5 mmol) of **12** in 75 ml of dry CH_2Cl_2 until the reaction mixture remained colored. The pyridine salts were removed by filtration, and the filtrate evaporated to dryness. The residue was column chromatographed on 50 g of Merck silica gel PF_{254} in $CHCl_3$–CCl_4 (4:1 v/v) under slightly increased pressure (about 10 cmHg) to afford 1.29 g (4.0 mmol, 81%) of **13** which was identical with the specimen described above.

3,3-Dimethylindoline-2-(*N*-methyl)carboxamide (14). To a solution of 1.01 g (5 mmol) of **3** in 100 ml of absolute ethanol at room temperature was added a trace of bromocresol green; after addition of 2 N methanolic HCl to a yellow end point (pH ≃ 3), the stirred mixture was supplied with 1.5 g (24 mmol) of sodium cyanoborohydride, and more HCl–methanol solution was added to maintain the yellow color. Stirring was continued for 30 min. Then the mixture was concentrated in vacuo, after which chloroform and water were added. The aqueous layer was washed with chloroform and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give 1.02 g (100%) of white crystals (mp 143–145 °C) homogeneous on TLC (12% EtOH/toluene): NMR δ 6.93–7.73 (m, 4 H, C_{4-7} H), 4.75 (m, 1 H, NH), 4.40 (d, 1 H, C_2 H), 3.23 (d, 3 H, NMe), 1.94 (s, 3 H, C_3 $C_\alpha H_3$), and 1.46 (s, 3 H, C_3 $C_\beta H_3$).

9,9a-Dihydro-1,9,9-trimethyl-2-methylene-3,10-diketopiperazine[1,2-*a*]indole (17). **4** (4.4 ml, 2.2 mmol) in CCl_4 (0.5 M) was added at room temperature to a stirred solution of 408 mg (2 mmol) of **14** and 285 mg (2.2 mmol) of diisopropylethylamine in 50 ml of dry tetrahydrofuran. After stirring for 16 h at room temperature, 200 ml of $CHCl_3$ was added, after which the reaction mixture was washed with 1 N HCl, 5% $NaHCO_3$, and water until neutral, and then dried (Na_2SO_4). A ^1H NMR spectrum indicated the presence of **15** and **16** in a ratio of 3:1, respectively. After filtration 1 ml of trifluoroacetic acid was added and the solution stirred for 1 h at room temperature. Then solid Na_2CO_3 was added, together with Na_2SO_4. Filtration, then concentration in vacuo, followed by column chromatography on 30 g of Merck silica gel PF_{254} in chloroform gave 425 mg (83%) of **17**, which showed only one spot on TLC (12% C_2H_5OH–toluene): mp 139–141 °C (CCl_4); NMR δ 8.45 (m, 1 H, C_5 H), 7.53 (m, 3 H, C_{6-8} H), 6.20 (d, 1 H, C=CH_α), 5.30 (d, 1 H, C=CH_β), 4.77 (s, 1 H, C_{9a} H), 3.90 (s, 3 H, NMe), 2.05 (s, 3 H, C_9 $C_\alpha H_3$), 1.52 (s, 3 H, C_9 $C_\beta H_3$).

Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.0; H, 6.2; N, 10.6.

9,9a-Dihydro-1,2,9,9-tetramethyl-2-mercapto-3,10-diketopiperazino[1,2-*a*]indole (18). A solution of 256 mg (1 mmol) of **17** in 25 ml of dry CH_2Cl_2 was allowed to react with H_2S in the presence of 200 mg of $ZnCl_2$ as described for the preparation of **12**. After filtration and removal of the solvent in vacuo, 290 mg of a glassy material was obtained, which showed only one, $AgNO_3$ positive, spot on TLC (R_f identical with that of **17**): NMR δ 8.43 (m, 1 H, C_5 H), 7.53 (m, 3 H, C_{6-8} H), 4.75 (S, 1 H, C_{9a} H), 3.70 (s, 3 H, NMe), 3.12 (s, br, 1 H, SH), 2.45 (s, 3 H, C_2 CH_3), 2.06 (s, 3 H, C_9 $C_\alpha H_3$), and 1.52 (s, 3 H, C_9 $C_\alpha H_3$).

9,9a-Dihydro-1,2,9,9-tetramethyl-2,9a-epithio-3,10-diketopiperazino[1,2-*a*]indole (20). A solution of 64 mg (0.2 mmol) of **13** and 57 mg (0.22 mmol) of triphenylphosphine in 15 ml of dry dioxane was stirred for 30 min at room temperature. Evaporation of the solvent in vacuo and column chromatography on 17 g of Merck silica gel PF_{254} in $CHCl_3$–CCl_4 (4:1 v/v) gave 54 mg (93%) of crystalline (mp 99–101 °C, CH_3OH) material which on TLC showed only one spot (R_f 0.58, 2% MeOH/CH_2Cl_2): ir ($CHCl_3$) 1721 cm^{-1} (CO); NMR δ 7.91 (m, 1 H, C_5 H), 7.60 (m, 3 H, C_{6-8} H), 3.32 (s, 3 H, NMe), 2.19 (s, 3 H, C_2 CH_3), 2.13 (s, 3 H, C_9 $C_\alpha H_3$), and 1.85 (s, 3 H, C_9 $C_\beta H_3$); mass spectrum (electron impact) *m/e* 288 (M^+), 273 ($M^+ - CH_3$), and 256 ($M^+ - S$); (chemical ionization, NH_3) 306 ($M + NH_4^+$, 100), 289 ($M + H^+$, 28), 276 ($M + NH_4^+ - 2CH_3$, 31), 274 ($M + NH_4^+ - S$, 7), 259 ($M + H^+ - 2CH_3$, 50), and 257 ($M + H^+ - S$, 14).

Anal. Calcd for $C_{15}H_{16}N_2O_2S$: C, 62.48; H, 5.59; N, 9.71. Found: C, 62.5; H, 5.7; N, 9.7.

9,9a-Dihydro-1,2,9,9-tetramethyl-2-methoxy-3,10-diketo-9a-mercaptopiperazino[1,2-*a*]indole (23). When the above reaction was performed in methanol instead of dioxane, another compound besides **20** (33%) was obtained after silica gel column chromatography. This product (63%) was assigned structure **23** on the basis of the following data: ir ($CHCl_3$) 1680 cm^{-1} (CO); NMR δ 8.40 (m, 1 H, C_5 H), 7.60 (m, 3 H, C_{6-8} H), 3.78 (s, 3 H, OCH_3), 3.56 (s, 1 H, SH), 3.45 (s, 3 H, NMe), 2.18 (s, 6 H, C_2 CH_3 + C_9 $C_\alpha H_3$), and 1.54 (s, 3 H, C_9 $C_\alpha H_3$); mass spectrum *m/e* 320 (M^+), 288, 273, 260, 256 ($M - SH - OCH_3$), 241, and 231.

Treatment of **23** with trifluoroacetic acid in CCl_4 gave quantitatively the mercaptoalkene **11**.

9,9a-Dihydro-1,2,9,9-tetramethyl-2,9a-epitrithio-3,10-diketopiperazino[1,2-*a*]indole (21). A solution of 47 mg (0.43 mmol) of SCl_2 in 3 ml of ethanol-free $CHCl_3$ was added dropwise to an ice-cooled, stirred solution of 140 mg (0.43 mmol) of **12** in 10 ml of ethanol-free $CHCl_3$. After stirring for 30 min at room temperature, the reaction mixture was washed with 5% $NaHCO_3$ solution and water until neutral and then dried (Na_2SO_4). Evaporation, followed by column chromatography on the residue on 20 g of Merck silica gel PF_{254} in $CHCl_3$–CCl_4 (4:1 v/v), yielded 133 mg (81% of crystalline material, mp 135–136 °C (CH_3OH–H_2O). The ^1H NMR spectrum indicated the presence of two isomers. On TLC (R_f 0.61, 2% MeOH/CH_2Cl_2) only one spot was visible: ir ($CHCl_3$) 1682 cm^{-1} (CO); NMR δ 8.51 and 8.76 (2 m, 1 H, C_5 H), 7.65 (m, 3 H, C_{6-8} H), 3.47 and 3.65 (2 s, 3 H, NMe), 2.38 and 2.42 (2 s, 3 H, C_2 CH_3), 2.12 (s, 3 H, C_9 $C_\alpha H_3$), 1.67 and 1.69 (2 s, 3 H, C_9 $C_\beta H_3$); mass spectrum (chemical ionization, NH_3) *m/e* 370 ($M^+ + NH_4^+$, 46), 353 ($M^+ + H^+$, 8), 338 ($M^+ + NH_4^+ - S$, 100), 321 ($M^+ + H^+ - S$, 37), 257 ($M + H^+ - 3S$, 72).

Anal. Calcd for $C_{15}H_{16}N_2O_2S_3$: C, 51.11; H, 4.58; N, 7.95. Found: C, 51.1; H, 4.8; N, 7.5.

9,9a-Dihydro-1,2,9,9-tetramethyl-2,9a-epitetrathio-3,10-diketopiperazino[1,2-*a*]indole (22). Dithiol **12** (140 mg, 0.43 mmol) was treated with S_2Cl_2 (58 mg, 0.43 mmol) in $CHCl_3$ as described for the preparation of **21**. Column chromatography on silica gel gave 122 mg (67%) of **22**, which, though homogeneous on TLC (R_f 0.59, 2% MeOH/CH_2Cl_2), resisted crystallization. An aqueous methanolic solution of **22** was found to be unstable at room temperature, as was shown by TLC: ir ($CHCl_3$) 1670 cm^{-1} (CO); NMR δ 8.55 (m, 1 H, C_5 H), 7.70 (m, 3 H, C_{6-8} H), 3.57 (s, 3 H, NMe), 2.41 (s, 3 H, C_2 CH_3), 21.9 (s, 3 H, C_9 $C_\alpha H_3$), and 1.69 (s, 3 H, C_9 $C_\beta H_3$); mass spectrum (electron impact) *m/e* 256 ($M^+ - S_4$) and 241 ($M^+ - S_4 - CH_3$); (chemical ionization, NH_3) *m/e* 402 ($M + NH_4^+$, 48), 385 ($M + H^+$, 83), 370 ($M + NH_4^+ - S$, 32), 353 ($M + H^+ - S$, 43), 338 ($M + NH_4^+ - S_2$, 22), 321 ($M + H^+ - S_2$, 32), 289 ($M + H^+ - S_3$, 5), and 257 ($M + H^+ - S_4$, 100).

Anal. Calcd for $C_{15}H_{16}N_2O_2S_4$: C, 46.8; H, 4.2; N, 7.3. Found: C, 46.7; H, 4.2; N, 7.0.

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Registry No.—**3**, 58788-11-7; **4**, 5704-66-5; **6**, 59888-42-5; **7**, 59888-43-6; **8**, 59888-44-7; **9**, 59888-45-8; **10**, 59888-46-9; **11**, 59888-47-0; **12**, 59888-48-1; **13**, 59888-49-2; **14**, 59888-50-5; **15**, 59888-51-6; **16**, 59888-52-7; **17**, 59888-53-8; **18**, 59888-54-9; **20**, 59888-55-0; **21**, 59888-56-1; **22**, 59888-57-2; **23**, 59888-58-3; ethyl 3,3-dimethylindolenine-2-carboxylate, 41296-09-7; methylamine, 74-89-5; thioacetic acid, 507-09-5.

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A New Systematic Degradation of Nicotine to Determine Activity at C-2′ and C-5′. The Pattern of Labeling in Nicotine and Nornicotine Formed from [2-^{14}C]Ornithine in *Nicotiana glutinosa*, and in Nicotine Obtained from *N. tabacum* Exposed to [^{14}C,^{13}C]Carbon Dioxide

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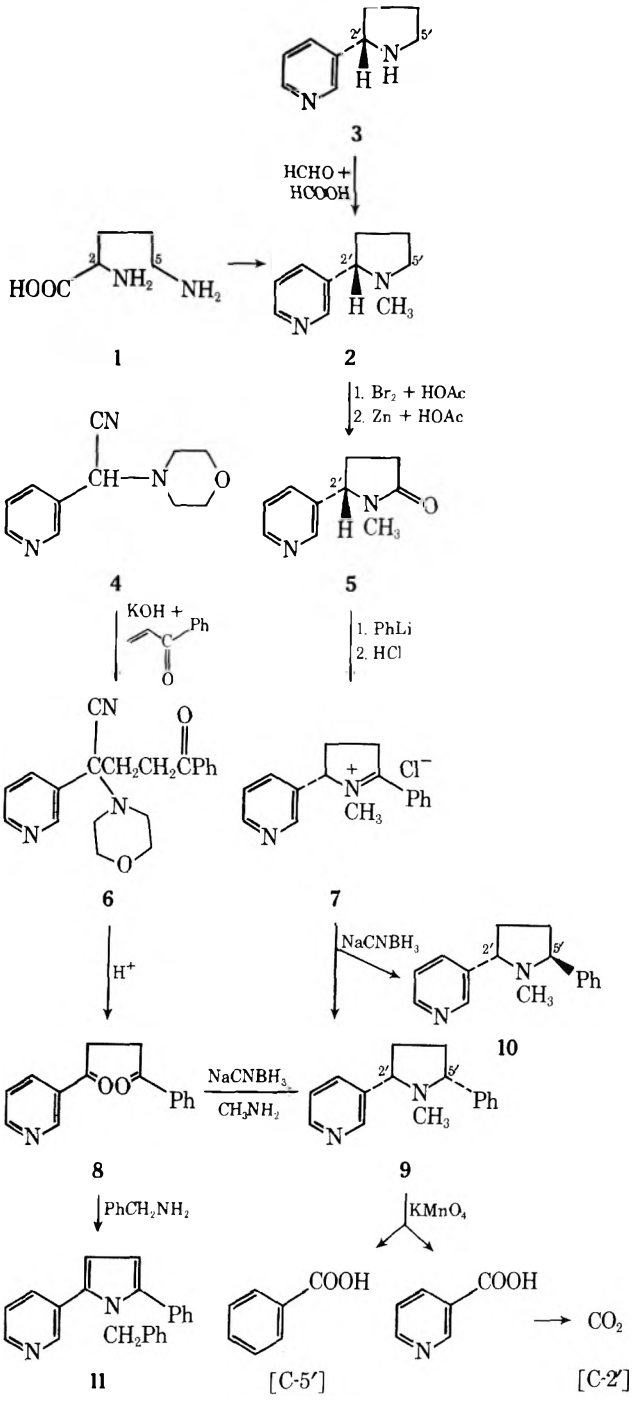
Radioactive nicotine has been degraded by the following sequence: nicotine → cotinine → *cis*-5′-phenylnicotine → benzoic acid [C-5′] + nicotinic acid → barium carbonate [C-2′]. The structure of 5′-phenylnicotine was confirmed by an unambiguous synthesis. On applying this degradation to nicotine and nornicotine isolated from *N. glutinosa* plants which had been fed [2-^{14}C]ornithine, equal labeling was found at C-2 and C-5′ of the pyrrolidine ring of both these alkaloids. Nicotine isolated from *N. tabacum* plants which had been exposed to [^{14}C,^{13}C]carbon dioxide also had equal labeling at C-2′ and C-5′. All these results are thus consistent with the formation of the pyrrolidine ring of nicotine and nornicotine from ornithine via a symmetrical intermediate.

It is more than 20 years since Byerrum[2] and I[3] first reported that ornithine (1) is a precursor of the pyrrolidine ring of nicotine (2). By chemical degradations,[4,5] it was established that [2-^{14}C]ornithine yielded nicotine equally labeled at C-2′ and C-5′.[6] These results led to the proposal that the pyrrolidine ring is formed from ornithine via putrescine, *N*-methylputrescine, and an *N*-methyl-Δ^1-pyrrolinium salt.[7] Indeed, enzymes which carry out these metabolic steps have been isolated from tobacco roots.[8] Symmetrical labeling of the pyrrolidine ring is a result of the intermediacy of free putrescine, a symmetrical compound. However, Rapoport and co-workers,[6,9] on the basis of several short-term feeding experiments with $^{14}CO_2$, have suggested that the formation of nicotine from ornithine, via a symmetrical intermediate, may be a minor or aberrant pathway. This proposal was made since, on occasions,[10] the exposure of tobacco plants to $^{14}CO_2$ led to unsymmetrical labeling of the pyrrolidine ring. In particular, unequal labeling was reported at C-2′ and C-5′. On the other hand, Byerrum and co-workers[11] found symmetrical labeling in the pyrrolidine ring of nicotine obtained from *N. glutinosa* and *N. rustica* plants fed $^{14}CO_2$.

It is generally accepted that nicotine is a precursor of nornicotine (3).[12,13] However, the pattern of labeling in nornicotine after feeding [2-^{14}C]ornithine to tobacco has been reported in only one publication,[14] and in this case it was claimed that the pyrrolidine ring of nornicotine was unsymmetrically labeled.[15]

In view of these conflicting results, and possible errors,[16,17] in the methods used for determining the pattern of labeling in the pyrrolidine ring of nicotine, we have now developed a

Scheme I. Degradation of Nicotine and Nornicotine



new degradative scheme, illustrated in Scheme I, whereby the activity at C-2′ and C-5′ can be unambiguously determined. Bromination of natural (−)-(2′*S*)-nicotine yielded 4′,4′-dibromocotinine which on reduction with zinc afforded (−)-(2′*S*)-cotinine (**5**).[18] Phenyllithium reacted with cotinine in tetrahydrofuran at −78 °C, presumably yielding, after acidification with hydrochloric acid, 1-methyl-2-phenyl-5-(3-pyridyl)-Δ^1-pyrrolinium chloride (**7**).[19] Reduction of this compound, without isolation, with sodium cyanoborohydride afforded a mixture of *cis*-(2′S)-5′-phenylnicotine (**9**) and *trans*-(2′S)-5′-phenylnicotine (**10**) in a ratio of 14:1, readily separated by TLC. Structures were assigned on the basis of their optical rotations, the cis isomer having the smaller specific rotation. The predominance of the cis isomer was expected since the bulky cyanoborohydride anion would approach the pyrrolinium salt **7** from the less hindered side. Reduction of **7** with sodium borohydride afforded a greater proportion of the trans isomer.[20] The structure of 5′-phenylnicotine was confirmed by an independent synthesis, also illustrated in Scheme I. Michael addition of the anion of α-morpholino-α-(3-pyridyl)acetonitrile (**4**)[21] to phenyl vinyl ketone afforded compound **6**, which on acid hydrolysis yielded 1-phenyl-4-(3-pyridyl)butane-1,4-dione (**8**). The structure of this diketone was confirmed by the formation of 1-benzyl-2-phenyl-5-(3-pyridyl)pyrrole (**11**) by reaction with benzylamine. Reductive amination of this diketone with methylamine and sodium cyanoborohydride[22] afforded racemic *cis*-5′-phenylnicotine as the major product, having an infrared spectrum identical with that of the optically active compound derived from (2′*S*)-cotinine. Oxidation of *cis*-5′-phenylnicotine with permanganate yielded a mixture of benzoic acid (representing the activity at C-5′ of nicotine) and nicotinic acid, readily separated on the basis of their solubilities in ether and dilute acid (see Experimental Section). Refluxing the nicotinic acid in quinoline in the presence of copper chromite yielded carbon dioxide (representing C-2′) and was collected as barium carbonate.[23] Heating nicotinic acid with calcium oxide afforded pyridine, assayed as its picrate. Activity at C-2′ was thus determined directly, and by the difference in activity between nicotinic acid and pyridine picrate.

This degradative scheme was carried out on nicotine and nornicotine obtained from *N. glutinosa* plants which were fed (*RS*)-[2-^{14}C]ornithine for 7 days. The nornicotine was converted to nicotine by the Eschweiler–Clark method.[12] The results recorded in Table I clearly indicate that the pyrrolidine rings of both nicotine and nornicotine were symmetrically labeled, equal activity being found at C-2′ and C-5′. We have also carried out this degradation on labeled nicotine obtained from *N. tabacum* plants which were fed $^{13}CO_2$ [97% ^{13}C] containing a tracer amount of $^{14}CO_2$.[24] This nicotine was also found to have equal labeling at C-2′ and C-5′.

We thus consider that these results corroborate previous work on the origin of the pyrrolidine ring of nicotine, and support the hypothesis that it is formed from ornithine via a symmetrical intermediate.

Experimental Section[25]

Conversion of Nicotine to Cotinine. The following oxidation is a modification of that previously described,[18] carrying out the reactions on a small scale. Nicotine diperchlorate (1.0 g) was dissolved in 80% (by volume) acetic acid (3 ml) and cooled to 0 °C, and a solution of bromine (1.2 ml) in 80% acetic acid (3 ml) slowly added with stirring during 1 h. The mixture was stirred overnight while the temperature was allowed to rise to room temperature. Water (10 ml) was added and the mixture heated on a steam bath until a clear red solution was obtained (i.e., until excess bromine had vaporized). On slow cooling dibromocotinine hydrobromide perbromide separated as orange needles (1.3 g). Zinc dust (1.5 g) was added, during 0.5 h, to a stirred suspension of this dibromo derivative in a mixture of water (10 ml), acetic acid (10 ml), and concentrated HCl (0.5 ml) at 20 °C. After stirring overnight, the filtered mixture was made basic with concentrated NH_3 and extracted with chloroform. The residue obtained on evaporation of the dried ($MgSO_4$) extract was distilled (140 °C, 0.01 mm) affording cotinine as a colorless, viscous oil (0.36 g, 74%).

Phenylation of (−)-(2′*S*)-Cotinine. Cotinine (3.25 g, 19 mmol) dissolved in tetrahydrofuran (10 ml) was added rapidly, under N_2, to a stirred ether solution of phenyllithium (20 mmol), prepared from bromobenzene (2.1 ml), lithium ribbon (0.28 g), and ether (10 ml), at −78 °C. After stirring for 1 h at −78 °C the mixture was allowed to warm up to room temperature during 3 h. Concentrated HCl (3 ml) was then added, and the mixture evaporated to small volume. The residue was dissolved in methanol (30 ml), sodium cyanoborohydride (2 g) added, and the mixture stirred at room temperature for 18 h. The solution was then evaporated to dryness, and the residue suspended in 5% NaOH and extracted with chloroform. The residue obtained on evaporation of this extract was dissolved in ether and extracted with 2 N HCl (3 × 20 ml). This acid extract was made basic with NaOH and extracted with chloroform. Evaporation of the dried ($MgSO_4$) extract yielded an oil which was subjected to preparative TLC on several plates of silica gel PF-254 (Merck), developing with a mixture of chloroform, ethanol, and concentrated NH_3 (200:10:1).

Table I. Activities of the Degradation Products of Nicotine and Nornicotine

	Orgin of the alkaloids					
	From *N. glutinosa* fed (*RS*)-[2-^{14}C]ornithine				From *N. tabacum* fed [^{14}C,^{13}C] CO_2[24]	
	Nicotine		Nornicotine		Nicotine	
	Specific activity, dpm/mmol × 10^{-5}	Relative specific activity	Specific activity dpm/mmol × 10^{-5}	Relative specific activity	Specific activity dpm/mmol × 10^{-6}	Relative specific activity
Nornicotine dipicrate			1.08 ± 0.02[a]	103		
Nicotine diperchlorate	3.12 ± 0.05	100	1.05 ± 0.02	100	1.30 ± 0.01	100
Cotinine dipicrate	3.18 ± 0.05	102	1.00 ± 0.02	95	1.31 ± 0.01	101
cis-5′-Phenylnicotine	3.13 ± 0.05	100	1.02 ± 0.03	97	1.31 ± 0.01	101
Nicotinic acid[b]	1.57 ± 0.03	50	0.50 ± 0.01	48	0.86 ± 0.01	66
Pyridine picrate	<0.02	0	<0.01	0	0.77 ± 0.01	59
Barium carbonate [C-2′]	1.54 ± 0.03	49	0.49 ± 0.01	47	0.087 ± 0.002	6.7
Benzoic acid [C-5′]	1.59 ± 0.03	51	0.48 ± 0.01	46	0.090 ± 0.002	6.9

[a] Standard deviation from the mean as determined from the average of at least three samples. [b] Obtained by two independent reactions: by the oxidation of nicotine,[23] and by the oxidation of *cis*-5′-phenylnicotine.

The zone with the highest R_f (0.8) was extracted with methanol affording *cis*-(2′*S*)-5′-phenylnicotine as a colorless, sweet-smelling oil, reminiscent of moist woods in the spring (1.24 g, 27%): $[\alpha]^{22}D$ −9.3°, $[\alpha]^{22}_{365}$ −67.2° (c 4.5, MeOH); uv (95% EtOH) λ_{max} 258 nm (ε 3690), 262 (3880), sh 268 (2960), in H^+ solution 260 (4960); mass spectrum *m/e* (rel intensity) 238 (36) M^+, 161 (100) M^+ − Ph, 160 (95) M^+ − pyridyl. In contrast to nicotine, this phenyl derivative is sparingly soluble in cold water. It afforded a diperchlorate as colorless plates from ethanol–ethyl acetate, mp 232–233 °C.

Anal. Calcd for $C_{16}H_{20}Cl_2N_2O_8$: C, 43.75; H, 4.59; N, 6.38. Found: C, 44.06; H, 4.82; N, 6.29.

Its dipicrate was obtained as fine yellow needles from ethanol, mp 152–153 °C.

Anal. Calcd for $C_{28}H_{24}N_8O_{14}$: C, 48.28; H, 3.47; N, 16.09. Found: C, 48.39; H, 3.64; N, 15.37.

The zone (R_f 0.7) immediately below that of the *cis*-5′-phenylnicotine was extracted with methanol, and yielded on evaporation *trans*-(2′*S*)-5′-phenylnicotine (89 mg, 2%) as a colorless oil: $[\alpha]^{22}D$ −122° (c 3.2, MeOH); uv (95% EtOH) λ_{max} 257 nm (ε 3540), 262 (3520), sh 268 (2680), in H^+ solution 260 (4870); mass spectrum *m/e* (rel intensity) 238 (30) M^+, 161 (100) M^+ − Ph, 160 (95) M^+ − pyridyl. It yielded a dipicrate, mp 184–185 °C.

Anal. Calcd for $C_{28}H_{24}N_8O_{14}$: C, 48.28; H, 3.47; N, 16.09. Found: C, 48.51; H, 3.62; N, 15.94.

Cotinine (0.62 g, 18%) was recovered from a lower zone (R_f 0.5) of the TLC. In a typical degradation of radioactive nicotine, the phenylation of cotinine was carried out on a 2-mmol scale and resulted in essentially the same yields of *cis*- and *trans*-5′-phenylnicotine. The use of commercially available phenyllithium dissolved in a 70/30 mixture of benzene and ether led to lower yields of phenylated product, and the results were erratic. In preliminary work, the reduction of the intermediate pyrrolinium salt **7** was carried out by refluxing a solution of this salt in ethanol with excess sodium borohydride for 10 min, followed by stirring at room temperature for 2 h. The ratio of the resultant *cis*- and *trans*-5′-phenylnicotine was 2:1.

1-Phenyl-4-(3-pyridyl)butane-1,4-dione (8). Phenyl vinyl ketone[26] (2.64 g, 20 mmol) dissolved in a mixture of ethanol (5 ml) and ether (15 ml) was added slowly under N_2 to a solution of α-morpholino-α-(3-pyridyl)acetonitrile[21] (4.26 g, 20 mmol) in a mixture of ethanol (10 ml) and ether (30 ml) cooled to −78 °C, to which had been previously added 0.5 ml of a methanolic solution of KOH (30%). After stirring for 1 h, the reaction mixture was allowed to warm to room temperature and stirred for an additional 12 h. The residue obtained on evaporation was warmed with a mixture of acetic acid (10 ml), tetrahydrofuran (3 ml), and water (5 ml) for 12 h at 50 °C. The solution was made basic with K_2CO_3 and extracted with chloroform. The residual oil obtained on evaporation of the dried (Na_2SO_4) extract was distilled (140 °C, 0.01 mm) affording a mixture of an oil (mainly pyridine-3-aldehyde) and a white solid (1.6 g, 33%). Crystallization of this solid from a mixture of benzene and ether afforded colorless prisms of the diketone 8: mp 97–98 °C; uv (95% EtOH) λ_{max} 243 nm (ε 19 200), sh 270 (4980), sh 278 (3930); ir (KBr) 1678 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity) 239 (21) M^+, 134 (17) $PyrCOCH_2CH_2$–, 133 (10) $PhCOCH_2CH_2$–, 106 (87) PyrCO–, 105 (100) PhCO–, 78 (74) Pyr–, 77 (79) Ph–.

Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.12; H, 5.63; N, 5.92.

***cis*-(*RS*)-5′-Phenylnicotine** The diketone 8 (239 mg, 1 mmol), methylamine hydrochloride (80 mg, 1.2 mmol), and sodium cyanoborohydride (200 mg) were stirred in methanol (5 ml) at room temperature. The reaction mixture was monitored periodically by TLC. The main product which was being produced was *cis*-5′-phenylnicotine, and only traces of the trans isomer were detected. After 5 days the reaction mixture was evaporated and the residue was suspended in dilute NaOH and extracted with chloroform. The residue obtained on evaporation of the dried ($MgSO_4$) extract was subjected to TLC (using the same solvent system as described previously) affording *cis*-(*RS*)-5′-phenylnicotine (123 mg, 52%) having an ir spectrum (neat) identical with that of *cis*-(2′*S*)-5′-phenylnicotine. It afforded a dipicrate, mp 233–234 °C. In general the melting points of the dipicrates of racemic nicotine derivatives are higher than those of the optically active derivatives. However, the difference in melting point is not usually as dramatic as in this case.

Anal. Calcd for $C_{28}H_{24}N_8O_{14}$: C, 48.28; H, 3.47; N, 16.09. Found: C, 48.16; H, 3.62; N, 15.72.

1-Benzyl-2-phenyl-5-(3-pyridyl)pyrrole (11). The diketone 8 (136 mg) was refluxed in benzene (5 ml) with benzylamine (0.3 ml) for 8 h. The residue obtained on evaporation was sublimed (100 °C, 0.001 mm) and crystallized from a mixture of benzene and ether, yielding the pyrrole 11 (156 mg, 88%) as colorless prisms: mp 116–117 °C; uv (95% EtOH) λ_{max} 304 nm (ε 13 350) very similar to that of 1-methyl-2,5-diphenylpyrrole,[27] 306 (18 750); mass spectrum *m/e* (rel intensity) 311 (15) M^+ +1, 310 (54) M^+, 219 (74) M − $PhCH_2$, 91 (100) $PhCH_2$–.

Anal. Calcd for $C_{22}H_{18}N_2$: C, 85.13; H, 5.83; N, 9.02. Found: C, 85.37; H, 6.00; N, 8.74.

Oxidation of *cis*-(2′*S*)-5′-Phenylnicotine. *cis*-(2′*S*)-5′-Phenylnicotine diperchlorate (106 mg) was dissolved in water (5 ml) at 35 °C. Sodium hydroxide (0.5 ml of a 10% solution) and potassium permaganate (150 mg) were added. After stirring for 1 h, additional permanganate (150 mg) was added and stirring continued overnight. Sulfur dioxide was passed into the reaction mixture until a clear solution was obtained. A continuous ether extraction of this solution yielded on evaporation a white solid which was extracted with cold ether (2 × 15 ml). This ether extract was washed with 2 N HCl (2 × 5 ml) and then dried (Na_2SO_4). The residue obtained on evaporation was sublimed affording benzoic acid (18.9 mg, 64%) which was crystallized from hot water. The initial residue, sparingly soluble in cold ether, was sublimed (120 °C, 0.001 mm) affording nicotinic acid (22.8 mg, 77%) which was crystallized from absolute ethanol.

The nicotinic acid was further degraded as previously described.[23] The barium carbonate obtained from the decarboxylation was assayed by dissolving in an aqueous solution of tetrasodium ethylenediamine tetraacetate.[28]

Feeding of (*RS*)-[2-^{14}C]Ornithine to *Nicotiana glutinosa* Plants and Isolation of the Alkaloids. (*RS*)-[2-^{14}C]Ornithine (2.7

mg, 1.56×10^8 dpm, New England Nuclear) dissolved in water was fed by the wick method to 40 3-month-old *N. glutinosa* plants growing in soil in a greenhouse (June). After 7 days the plants (fresh wt 2.8 kg) were harvested (residual activity not absorbed by the plants: 0.07%), macerated with chloroform and concentrated NH_3, and worked up as previously described.[29] The crude alkaloids (1.76×10^6 dpm, 1.1% incorporation) were separated by TLC,[29] affording nornicotine (187 mg), crystallized to constant activity as its dipicrate (1.08×10^5 dpm/mmol), and nicotine (472 mg), assayed as its diperchlorate (3.12×10^5 dpm/mmol). The anabasine (3.1 mg) and anatabine (16.6 mg) purified as their dipicrates had negligible activity ($<10^3$ dpm/mmol).

Registry No.—*RS*-**1**, 616-07-9; **2**, 54-11-5; **2** diperchlorate, 59888-66-3; **3**, 494-97-3; **3** dipicrate, 6255-01-2; **4**, 36740-09-7; **5**, 486-56-6; **5** dipicrate, 59888-69-6; **8**, 49835-54-3; **9**, 59888-67-4; **9** diperchlorate, 59888-68-5; **9** dipicrate, 59951-82-5; **10**, 59951-83-6; **10** dipicrate, 59980-68-6; **11**, 59888-70-9; nicotinic acid, 59-67-6; pyridine picrate, 3480-66-8; barium carbonate, 513-77-9; benzoic acid, 65-85-0; CO_2, 124-38-9; phenyl vinyl ketone, 768-03-6; *cis*-(*RS*)-5′-phenylnicotine, 59951-84-7; *cis*-(*RS*)-5′-phenylnicotine dipicrate, 59951-85-8; benzylamine, 100-46-9.

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(1) Contribution No. 143 from this laboratory. This investigation was supported by Research Grant GM-13246 from the National Institutes of Health, U.S. Public Health Service, and also by Grant 929 from The Council for Tobacco Research—U.S.A., Inc. Presented in part at the 172nd National Meeting of the American Chemical Society, San Francisco, Calif., Sept 1976.
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(15) In two separate experiments (lasting 24 and 30 days) (*RS*)-[2-^{14}C]ornithine was fed to isolated roots of *N. rustica* yielding radioactive nicotine and nornicotine. The nicotine on oxidation yielded nicotinic acid having 49% of the specific activity of the nicotine, all this activity being on the carboxyl group. This result was thus consistent with previous work, indicative of symmetrical labeling of the pyrrolidine ring. However, the nornicotine on oxidation yielded nicotinic acid having 68% of the specific activity of the nornicotine. I believe that this result is suspect since the nornicotine dipicrate, which had been crystallized five times to constant specific activity, was reported to lose half its specific activity when converted to its diperchlorate! The rationalization which the authors offered for the loss of this activity, namely that the plant was producing racemic nornicotine, which then lost activity on dilution with L-nornicotine and subsequent crystallization of its diperchlorate, seems improbable.
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(24) This labeled nicotine was kindly given to me by Professor C. R. Hutchinson, School of Pharmacy, University of Wisconsin, The labeled sample used in our degradation was obtained from *N. tabacum* plants exposed to [^{14}C,^{13}C]CO_2 for 14 h, and then allowed to grow for an additional 226 h in a normal atmosphere. The distribution of ^{13}C in this sample was determined by means of ^{13}C NMR: C. R. Hutchinson, M-T. S. Hsia, and R. A. Carver, *J. Am. Chem. Soc.*, **98**, 6006 (1976). Our results for the distribution of ^{14}C in this sample (see Table I) are in good agreement with the distribution of ^{13}C found by Hutchinson: pyridine ring, 62; C-2′, 6; C-5′, 7%.
(25) Melting points are corrected. Elementary analyses were performed by Clark Microanalytical Laboratory, Urbana, Ill. Mass spectra were determined by Dr. Roger Upham and his assistants at the University of Minnesota on an AEI-MS-30 instrument. Optical rotations were determined on a Perkin-Elmer 241 polarimeter. Ultraviolet spectra were determined on a Cary 11 spectrometer. Radioactivity measurements were carried out in a Nuclear Chicago liquid scintillation Mark II counter, using as a solvent dioxane–ethanol with the usual scintillators.[23]
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Aphylline, Epiaphylline, 10,17-Dioxosparteine, Gramine, and Other Unexpected Alkaloids from *Lupinus hartwegii*

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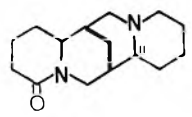
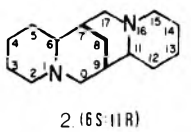
In addition to lupanine (**1**) and 13-hydroxylupanine, originally reported in flowering plants of *L. hartwegii*, four oxosparteines, aphylline (**3**), epiaphylline, 13-hydroxyaphylline (virgiline), and 10,17-dioxosparteine, not previously reported in any *Lupinus* species were isolated. 4-hydroxylupanine (nuttaline), α-isolupanine (**6**), and gramine (**7**) were also present in addition to five other partially characterized alkaloids. Even though carefully looked for, no sparteines **2**, **5**, **8**, lupinine, or angustifoline were detected.

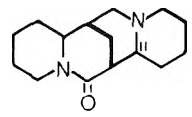
Lupanine (**1**), the major alkaloid reported in *Lupinus hartwegii*,[1] is viewed as being an oxidation product of sparteine (**2**).[2-4] However, this plant apparently forms little or no sparteine, but has been genetically crossed with *L. arboreus*, whose alkaloid is sparteine, to produce hybrids whichcan form both **1** and **2**.[5]



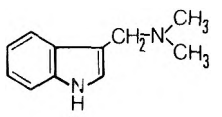
1. (11R)
6. (11S)



2. (6S:11R)
5. (6S:11S)
8. (6R:11R)



3. (11R)
4. (11S)



7

This apparent genetic separability of the ability to form **1** or **2** is consistent with our conclusion from $^{14}CO_2$ pulse labeling studies on three other *Lupinus* species, that sparteine and lupanine may be synthesized independently of one another.[6] These and other $^{14}CO_2$ studies[7] also revealed the presence of several kinetically interesting (rapidly turning over) components in the alkaloid extracts, one of which (unknown A) appeared to be present in *L. hartwegii* in significant amounts.

Therefore, as part of a study on the biosynthesis of lupanine from $^{14}CO_2$,[8] an investigation was undertaken of the alkaloids in this plant using freshly harvested material to (1) determine whether any sparteine was present; (2) confirm lupanine as the major alkaloid; (3) determine the structure of A; and (4) characterize as many other alkaloids as possible.

Results and Discussion

An examination of the basic extract of fresh 6 week old plants of *Lupinus hartwegii* by TLC indicated the presence of at least ten alkaloids. By the sequential use of TLC, GLC, and mass spectrometry 14 alkaloids were purified and characterized. The presence of lupanine and 13-hydroxylupanine (alkaloids C and E, respectively), the only alkaloids previously reported in this plant,[1] was confirmed although the latter was present in very small amounts (Table I). Though carefully looked for there was no trace of sparteine or the bicyclic base lupinine, which is consistent with our recent demonstration that this species cannot form either alkaloid at this stage of development when lupanine formation from $^{14}CO_2$ is very active.[8]

Alkaloids A1 and a2, both having the composition $C_{15}H_{24}NO$, gave mass spectra very similar to those reported for the HBr salts of the 10-oxosparteines[9] but markedly different from that of 17-oxosparteine.[10] The presence of M − CO fragments in the mass spectra of both, characteristic of 10 and 17-oxosparteines,[9] was confirmed by high-resolution mass spectrometry. A1 was unchanged under mild catalytic hydrogenation conditions contrary to that reported for aphylline (**3**)[11] but was completely converted to α-isosparteine (**5**) under more drastic conditions, confirming it to be epiaphylline (**4**). Alkaloid A2, on the other hand, was completely reduced under mild conditions to sparteine, confirming it to be aphylline.[11]

Alkaloid A3 gave a MS with an apparent M^+ at *m/e* 246 but no M − CO fragment, clearly different from that reported for 5,6-dehydrolupanine[12] but similar to that of 11,12-dehydrolupanine.[10] The instability of this substance to air is also typical of 11,12- and other dehydrolupanines[13,14] and further work on this substance when available would be of interest, since only one fully characterized dehydrolupanine has been reported to date while at least 12 such compounds are possible and implicated as possible intermediates in the biosynthesis of this group of alkaloids.[7]

GLC of zone B revealed in addition to α-isolupanine (**6**, B1) two additional components. The MS of B2 was unlike that reported for any quinolizidine alkaloid, with an apparent M^+ at *m/e* 264 and no M − CO fragment, suggestive of a hydroxylupanine but clearly different from that of 4-hydroxylupanine (D3) or 13-hydroxylupanine (E), both also found in this plant. An unusual M − 41 fragment confirmed by a metastable at *m/e* 188.4 was prominent. Again insufficient sample prevented further analysis.

Alkaloid B3 gave a weak iodoplatinate reaction observed for 17-oxolupanine[15] but was distinguishable from the latter by GLC (Table I) and by MS.[10] A MS identical with that reported for 10,17-dioxosparteine[9] and reduction of B3 to 17-oxosparteine, as would be expected if the bridgehead hydrogen at C-6 were cis to the methylene bridge,[16] confirmed its structure.

Zone D yielded five components on GLC, the major one proving to be identical with nuttaline (4-hydroxylupanine). This is the first report of its occurrence since it was first isolated from *L. nuttallii*.[17] The MS of D2 with an apparent M^+ at *m/e* 264 differed from that reported for any lupin alkaloid or alkaloid B2. The presence of apparent M − H_2O and M − CO fragments at *m/e* 246 and 236, respectively, suggested that it might be a hydroxyaphylline, which was confirmed by comparison with an authentic sample of virgilline (13-hydroxyaphylline). This is the first report of this alkaloid in any other species since its original isolation from *Virgilia orboides*.[18]

The three remaining alkaloids of this group, D3, D4, and D5, all had the longest retention times on GLC of any of those isolated but less than that of *O*-(2-pyrrolylcarbonyl)virgiline (Table I). They also had unusually low R_f's in TLC (system B). Only D5 was present in sufficient amounts to permit any further examination. The MS of D5 revealed an apparent M^+ at *m/e* 378. An extremely large metastable at *m/e* 204.5 confirmed the M − 100 transition to *m/e* 278 (base peak) while

Table I. Chromatographic Properties of Standard Alkaloids and Those of 6 Week Old *Lupinus hartwegii*

Compd[b]	Gas-liquid chromatography[a] t_R, min	Alkaloid[c]	% [d]	R_f on TLC system A	B	C
α-Isosparteine	3.5			0.07	0.18	0.44
Sparteine	4.3			0.11	0.62	0.46
β-Isosparteine	5.8			0.08	0.44	0.43
Gramine	6.5[e]	E1	18.0	0.16	0.60	0.73
17-Oxosparteine	24.5			0.87	0.86	0.82
Epiaphylline	25.5	A1	6.0	0.88	0.91	0.70
α-Isolupanine	27.5	B1	1.3	0.80	0.85	0.52
Lupanine	28.5	C1	54.1	0.72	0.85	0.52
Unidentified	29.5	B2	0.5	0.78	0.88	0.49
Aphylline	30.0	A2	4.0	0.85	0.90	0.61
Nuttalline	30.5	D1	9.0	0.58	0.08	0.41
Unidentified	30.7	A3	0.2	0.85		
13-Hydroxylupanine	39.5	E2	0.2	0.35	0.44	0.35
10,17-Dioxosparteine	40.5	B3	0.3	0.82		
Virgiline	41.0	D2	1.1	0.60	0.52	0.45
17-Oxolupanine	43.0			0.84	0.85	0.88
Unidentified	52.5	D3	0.1	0.44	0.05	
Unidentified	54.5	D4	0.2	0.46	0.05	
Unidentified	68.5	D5	5.0	0.50	0.07	0.56
O-(2-Pyrrolylcarbonyl)virgiline	110.0[f]			0.86	0.94	0.76

[a] Ten percent QF-1 column; see text for conditions. [b] Arranged in order of increasing retention times on GLC. [c] Letter and number designations explained in text. [d] Percent of total plant alkaloids calculated from GLC peak areas and the relative weights of the alkaloids eluted from TLC. [e] Most of the injected alkaloid decomposed on GLC. [f] 250 °C isothermal.

M − 17 losses from both the *m/e* 378 and 278 peaks were confirmed by metastables at *m/e* 343 and 245. Though the compound was suspected of being an ester of a hydroxylupanine, no alkaloid could be recovered from even mild alkaline hydrolysis generally employed to characterize a number of esters of virgiline and 13-hydroxylupanine.[18,19] This apparent instability of the parent alkaloid under alkaline conditions is reminiscent of 5,6-dehydrolupanine[7] and would appear to rule out 13-hydroxylupanine or virgiline as the parent alkaloid. Further speculation would be fruitless in the absence of additional data.

The decomposition of the major alkaloid from zone F during GLC as well as its low R_f on TLC (system A) suggested the presence of a highly polar compound(s). The MS of the crystalline material indicated a single compound with an apparent M^+ at *m/e* 174, having the composition $C_{11}H_{14}N_2$. Its fragmentation pattern was unlike that of any quinolizidine alkaloid but was characteristic of a substituted indole.[20] This compound was identical with gramine (7), which, though not a typical lupin alkaloid, has been reported in *L. luteus*[21] and *L. hispanicus*.[22,23] Seeds of *L. hartwegii* contained only traces of gramine which increased steadily during growth so that by flowering, it exceeded the amount of lupanine. Finally gramine proved to be different from the previously reported "unknown A".[7]

The presence of aphylline was somewhat surprising since it has never been reported in any legume but rather from *Anabasis aphylla* (family *Chenopodiaceae*).[24] On the other hand, neither epiaphylline nor 10,17-dioxosparteine have been reported in any plant. The apparent absence of the tricyclic base angustifoline is interesting as it is thought to be an oxidation product of 13-hydroxylupanine[4] and their co-occurrence has been commonplace.[25] The taxonomic significance of this unusual alkaloid spectrum would be difficult to assess at present since *L. hartwegii* is not a wild species but a highly crossbred cultivar. Also, since with the exception of our recent studies on fresh plant material[13] most alkaloid reports are from dried flowering plants, many species on reexamination may yield a more surprising alkaloid spectrum.

Since sparteine, α-isosparteine, and β-isosparteine (8) are key compounds in the establishment of the basic ring skeleton and stereochemistry of many alkaloids in this family, it is of interest that all three may be easily separated by GLC or TLC (system B) (Table I) and may be distinguished by their mass spectra.[10,12] Although to date, with the exception of β-isosparteine and lupanoline,[26] no alkaloids with the trans,trans configuration have been isolated from plants, without this information, it could not have been ruled out in the present investigation, given the small amounts of alkaloid or their reduction products.

Finally the GLC behavior of the isomeric pairs sparteine/α-isosparteine and aphylline/epiaphylline was consistent with that observed for lupanine/α-isolupanine and reported for anagyrine/thermopsine,[15] the cis,cis isomer always emerging prior to that with the cis,trans configuration. This observation, together with the clear resolution of the three sparteine isomers, would seem to justify a prediction that all three possible isomers of any alkaloid of this basic skeleton would be resolvable by GLC under similar conditions.

Experimental Section

All solvents were reagent grade, redistilled through a 70-cm column filled with glass helices.

Chromatographic Methods. Three systems previously described[15] and designated as A, B, and C (silica gel G, basic alumina, and cellulose, respectively) were used. Alkaloid zones were located by spraying with iodoplatinate reagent.[27] GLC was carried out using the apparatus, column, and conditions described earlier[13] except that 2-ft glass columns were used and the oven was programmed immediately after sample injection at 2 °C/min. Collection of individual effluent peaks for spectroscopic examination, rechromatography, etc., was achieved as described earlier.[13,15]

Reference Compounds. With the exceptions listed below, all authentic reference alkaloids, their purity, identity, and behavior on all the above chromatographic systems have been described previously.[13,15] An authentic sample of virgiline (13-hydroxyaphylline) and *O*-(2-pyrrolylcarbonyl)virgiline were kindly supplied by Dr. E. P. White of the New Zealand Department of Agriculture, Hamilton, New Zealand. Both were purified by TLC, then by GLC. α-Isosparteine was synthesized in 90% yield by catalytic hydrogenation of thermopsine[28] and purified by preparative TLC (system A), then by GLC. β-Isosparteine was a gift from Dr. M. Carmack, Department of Chemistry, University of Indiana, Bloomington, Ind.

The three isomers of sparteine, crucial to establishing the basic ring structure and stereochemistry of several alkaloids, were separable by GLC or TLC (Table I). Their, MS, published in detail elsewhere,[12,29] while giving similar fragmentation patterns, showed significantly different intensities of the major ions. Sparteine: *m/e* 137 (100), 234 (81), 98 (78), 193 (40), 136 (31), 97 (30). α-Isosparteine: *m/e* 98 (100), 137 (54), 234 (52), 136 (28), 97 (26), 193 (18). β-Isosparteine: *m/e* 137 (100), 98 (99), 234 (70), 97 (62), 136 (46), 193 (31).

Spectroscopic Methods. All integer MS were recorded at 70 eV, using an AEI MS 12 instrument. Samples contained in glass capillary tubes were directly inserted by means of a probe into the ion source. High-resolution mass spectra were carried out by Professor A. M. Hogg, Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada. The uv absorbtion spectra were determined in 95% ethanol using a Cary Model 15 instrument. The NMR spectra were determined in $CDCl_3$, with tetramethylsilane as an internal reference, using a Varian HA-100 instrument.

Plant Material. Seeds of *L. hartwegii* were purchased from Herbst Bros., Seedsmen, Brewster, N.Y. The identity of plants grown to flowering was kindly checked by Dr. A. Skoglund of the Crop Science Department, and a voucher specimen, grown to flowering, is on file at the W. P. Fraser Herbarium at the University of Saskatchewan. All plants were grown in vermiculite in a controlled environment chamber under conditions described earlier.[7]

Isolation and Characterization of Plant Alkaloids. Extraction. Freshly harvested, 6 week old plants (640 g) were extracted immediately. Whole plants washed free of vermiculite were homogenized and extracted for basic compounds as described earlier.[13] The pale yellow alkaloid residue, 905 mg as acetate salts, was dried and stored under nitrogen at 0 °C. Recovery of all the reference alkaloids by this scheme was greater than 90%.[13,15]

Identification and Estimation of Alkaloids. Preparative TLC (system A) revealed the presence of eight to ten components. The TLC plates were divided into six zones, designed A–F, visualized by iodoplatinate reagent, collected with a Desaga zone collector, and eluted with 0.5 N HCl and enough sodium sulfite to dispel any purple color. Each of the six fractions was reextracted for basic compounds, then in turn analyzed by GLC, the alkaloids collected,[13] and designated by zone and order of elution from GLC (Table I). The purity of each GLC peak was checked by rechromatography on GLC, all three TLC systems, and by MS.

A1 (Epiaphylline), A2 (Aphylline), and A3. The alkaloids recovered from zone A, then collected from GLC, yielded 30 mg of A1 (white crystals), 20 mg of A2 (colorless liquid), and 1 mg of A3 (pale yellow liquid, rapidly turned red-brown in air). A3, appearing as a shoulder following A2, was freed of any residual A2 by rechromatography on GLC at 190 °C isothermal.

A1: MS M^+ *m/e* 248 (70), 247 (46), 220 (45), 137 (47), 136 (100), 98 (44), 97 (53), 96 (45), published in detail;[28] high-resolution MS M^+ 248.1884 (calcd for $C_{14}H_{24}N_2O$, 248.1889), M − 28 220.1938 (calcd for $C_{14}H_{24}N_2$, 220.1940). A1 (5 mg) was recovered unchanged after hydrogenation over PtO_2 in 1 N HCl at STP for 12 h. Rehydrogenation at 80 °C, 500 psig, yielded 4 mg of a single product identical with α-isosparteine by TLC (system B), GLC, and MS. 17-Oxosparteine was unchanged under either of these hydrogenation conditions.

A2: MS M^+ *m/e* 248 (80), 247 (45), 220 (33), 137 (49), 136 (100), 98 (34), 97 (47), 96 (37), published in detail;[29] high-resolution. MS M^+ 248.1884 (calcd for $C_{15}H_{24}N_2O$, 248.1889), M − 28 220.1938 (calcd for $C_{14}H_{24}N_2$, 220.1940). Hydrogenation of 5 mg of A2 over PtO_2 in 1 N HCl at STP for 12 h gave 4 mg of a single product identical with sparteine by TLC (system B), GLC, and MS.

A3: MS M^+ *m/e* 246 (100), 245 (27), 149 (19), 134 (26), 86 (37), 55 (18). See Table I for TLC and GLC behavior. Insufficient sample was present to characterize further.

B1 (α-Isolupanine), B2, and B3 (10,17-Dioxosparteine). Approximately 6.5 mg of B1 (white crystals), 2.5 mg of B2 (colorless liquid), and 1.5 mg of B3 (colorless liquid) were collected from GLC

of zone B. B1 and B2 were separated from one another on GLC at 200 °C, isothermal. B1 was homogeneous and indistiguishable from an authentic sample of α-isolupanine by TLC, GLC, and MS.[12] B2: MS M+ *m/e* 264 (3), 228 (11), 224 (15), 223 (100), 108 (26), 96 (11), 58 (51), metastables 188.4, 73.5, and 52.3. The sample was not further characterized. B3: MS M+ *m/e* 262 (88), 152 (52), 150 (100), 84 (70), 55 (29), published in detail.[29] Catalytic reduction of 0.5 mg of B3 in 1 N HCl, 500 psig at 10 °C for 24 h, yielded a single product identical by TLC, GLC, and MS with an authentic sample of 17-oxosparteine.

C (Lupanine). A substance (272 mg) was collected from zone C which was homogeneous and identical on all chromatographic systems and by MS[12] with an authentic sample of lupanine. This compound decreased from 85% of the total alkaloid in the seeds to about 27% at flowering.

D1 (Nuttalline), D2 (Virgiline), D3, D4, and D5. D1 (45 mg), D2 (5.5 mg), D3 (0.5 mg), D4 (1.0 mg), and D5 (25 mg), all colorless liquids, were collected by GLC of the alkaloids eluted from zone D. Angustifoline, if present, should have been found in this zone[15] but none was detected. D1 was homogeneous and indistinguishable by TLC, GLC, or MS[10] from an authentic sample of nuttalline (4-hydroxylupanine). D2 was homogeneous on all TLC systems and by GLC. MS M+ *m/e* 264 (35), 246 (24), 236 (34), 154 (25), 153 (74), 152 (100), 123 (26), 84 (51), 55 (31), was indistinguishable from that of an authentic sample of virgiline (10-oxo,13-hydroxysparteine/13-hydroxyaphylline).[29]

D3 and D4 were present in amounts only sufficient to determine their GLC and TLC behavior. D5 was homogeneous on all TLC systems and GLC: MS M+ *m/e* 378 (6), 361 (3), 279 (44), 278 (100), 261 (16), 148 (10), 134 (20), 55 (21). A very large metastable appeared at *m/e* 204.5 with others at *m/e* 343, 245, and 64.7. Alkaline hydrolysis of 4 mg of D5 in 1 N methanolic NaOH at 100 °C for 2 h yielded no recoverable basic material. No basic material was recoverable even after hydrolysis for only 20 min at 50 °C.

E (13-Hydroxylupanine). A substance (1 mg) collected from zone E was homogenous and identical on all TLC systems, GLC, and by MS[12] with an authentic sample of 13-hydroxylupanine. Lupinine, if present, should have been found in this zone[15] but none was detected.

F (Gramine). Sparteine, if present, should have been detected in zone F, but was not. However, 90 mg of a substance was collected which was homogenous on all TLC systems but showed signs of severe decomposition on GLC. Recrystallization from hot acetone gave 85 mg of a white material, mp 128–129 °C. Authentic gramine, similarly recrystallized, had mp 132 °C (lit.[30] 134 °C). MS M+ *m/e* 174 (23), 131 (19), 130 (100), 77 (13), 45 (10), 44 (23) was identical with that of gramine,[29] with metastables at *m/e* 126, 98.6, 81.7, and 57.6; λ_{max} (EtOH) 218 nm (log ε 3.4); ν_{max} 3480 cm^{-1} (s, NH stretch); NMR δ 2.30 s (6 H), 3.70 s (4 H), 7.2 m (4 H); high-resolution MS *m/e* 174.1150 (calcd for $C_{11}H_{14}N_2$; 174.1157), 131.0732 (calcd for C_9H_9N, 131.0735), 103.0540 (calcd for C_8H_5N, 103.0547), 77.0392 (calcd for C_6H_5, 77.0391).

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Registry No.—α-Isoparteine, 446-95-7; sparteine, 90-39-1; β-isosparteine, 24915-04-6; gramine, 87-52-5; 17-oxosparteine, 489-72-5; epiaphylline, 1218-51-5; α-isolupanine, 486-87-3; lupanine, 550-90-3; aphylline, 10159-81-6; nuttalline, 23360-87-4; 13-hydroxylupanine, 15358-48-2; 10,17-dioxosparteine, 52717-73-4; virgiline, 2636-61-5; 17-oxolupanine, 4697-83-0; *O*-(2-pyrrolylcarbonyl)virgiline, 18526-91-5.

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Ring C Conformation of 6β-Naltrexol and 6α-Naltrexol. Evidence from Proton and Carbon-13 Nuclear Magnetic Resonance[1]

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A series of acetate derivatives of 6β-naltrexol and 6α-naltrexol were prepared and examined by ^1H and ^{13}C NMR. The results of this investigation indicated that ring C of these compounds was in the chair conformation. Moreover, spectral assignments were noted which should be useful in examining the ring C conformation of other 14-hydroxy-7,8-dihydroisomorphine and 14-hydroxy-7,8-dihydromorphine compounds.

Naltrexone (*N*-cyclopropylmethyl-14-hydroxy-7,8-dihydronormorphinone, **1**) is a potent narcotic antagonist[3] which currently shows considerable promise for the treatment of opiate dependence in man. Studies in several laboratories have shown that 6β-naltrexol (**2a**) is the major urinary metabolite of naltrexone in man[4-7] and six species of laboratory animals.[7-9] 6α-Naltrexol (**3a**), on the other hand, is present in only trace amounts in the urine of two species of laboratory animals.[7] However, in vitro reduction of naltrexone using the soluble fraction of chicken liver homogenates yielded only **3a**.[5] The pharmacology of **2a** and **3a** is presently under investigation in several laboratories.

Initial chemical[4] and ^1H NMR[5] examination of **2a** and **3a** suggested that ring C of each compound was in the chair conformation with the 6β-hydroxyl substituent being equatorial and the 6α-hydroxyl substituent being axial. This assignment was confirmed by a later ^1H NMR study of **2a** and **3a** and their respective 3,6,14-triacetates (**2e** and **3e**),[7] and by the ^{13}C NMR chemical shifts reported for **2a** and **3a**.[10] 6β-Naltrexol and 6α-naltrexol are, therefore, conformationally similar to other 7,8-dihydroisomorphine and 7,8-dihydromorphine compounds.

As a result of the continuing interest in naltrexone and its biotransformation products, we undertook a ^1H and ^{13}C NMR examination of several acetate derivatives of **2a** and **3a**. Our purpose was to correlate spectral assignments with the ring C conformation. We believe the results reported below to be of general applicability to other 14-hydroxy-7,8-dihydroisomorphine and 14-hydroxy-7,8-dihydromorphine compounds.

In a recent report Hahn and Fishmann presented a similar ^1H NMR study on the 3,6-diacetate and 3,6,14-triacetate derivatives (**5b** and **6b**) of 6β-naloxol (**5a**) and 6α-naloxol (**6a**).[11] We also prepared compounds **5b** and **6b**, examined the ^1H NMR spectra, and compared our results with the earlier ones.

Results and Discussion

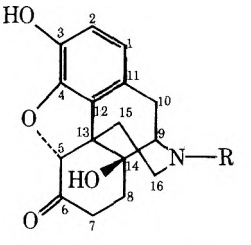
Sample Synthesis. 6β-Naltrexol (**2a**) was prepared by reducing naltrexone (**1**) with formamidinesulfinic acid in alkaline medium.[12] 6α-Naltrexol (**3a**) was obtained by reducing **1** with either sodium borohydride in tetrahydrofuran[13] or lithium tri-*sec*-butylborohydride[12,14] in tetrahydrofuran at −78 °C.[7] In our hands both reagents gave 6α-naltrexol (**3a**) contaminated with traces of the 6β epimer which could be removed by chromatography or recrystallization.

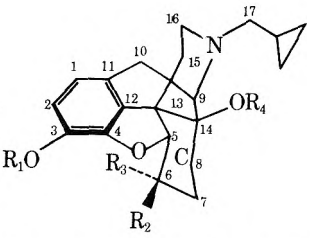
Acetylation of **2a** and **3a** with acetic anhydride and pyridine at room temperature overnight gave the corresponding 3,6,14-triacetates **2e** and **3e**. Acetylation with the same reagents at 0 °C for 1 h yielded the 3,6-diacetates **2d** and **3d**. In the case of **3a**, the 3,6-diacetate was contaminated with 15–20% of the 3,14-diacetate.[15] Hydrolysis of **2d** with 1 equiv of potassium carbonate in methanol afforded 6β-naltrexol 6-monoacetate (**2c**). Application of the same conditions to **3d** afforded only 6α-naltrexol. Sodium borohydride reduction of 14-acetoxynaltrexone gave 6α-naltrexol 14-monoacetate (**3c**). The two 3-monoacetates **2b** and **3b** were prepared by a standard procedure.[16,17]

6β-Naloxol (**5a**)[12] and 6α-naloxol (**6a**)[11] were prepared by the reduction of naloxone (*N*-allyl-14-hydroxy-7,8-dihydronormorphinone, **4**) with respectively formamidinesulfinic acid and lithium tri-*sec*-butylborohydride. The corresponding 3,6,14-triacetates **5b** and **6b** were prepared by the same procedure used to make **2e** and **3e**.

The various compounds examined in our study are summarized in Chart I.

Chart I

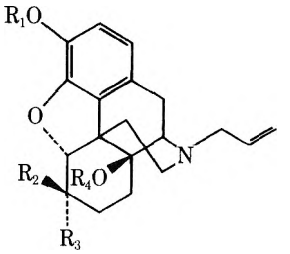




1, R = CH_2-c-C_3H_5

4, R = $CH_2CH{=}CH_2$

2a, $R_1 = R_3 = R_4 = H$; $R_2 = OH$
b, R_1 = Ac; $R_2 = OH$; $R_3 = R_4 = H$
c, $R_1 = R_3 = R_4 = H$; $R_2 = OAc$
d, R_1 = Ac; $R_2 = OAc$; $R_3 = R_4 = H$
e, $R_1 = R_4$ = Ac; $R_2 = OAc$; $R_3 = H$
3a, $R_1 = R_2 = R_4 = H$; $R_3 = OH$
b, R_1 = Ac; $R_2 = R_4 = H$; $R_3 = OH$
c, $R_1 = R_2 = H$; $R_3 = OH$; R_4 = Ac
d, R_1 = Ac; $R_2 = R_4 = H$; $R_3 = OAc$
e, $R_1 = R_4$ = Ac; $R_2 = H$; $R_3 = OAc$



5a, $R_1 = R_3 = R_4 = H$; $R_2 = OH$
b, $R_1 = R_4$ = Ac; $R_3 = H$; $R_2 = OAc$
6a, $R_1 = R_2 = R_4 = H$; $R_3 = OH$
b, $R_1 = R_4$ = Ac; $R_2 = H$; $R_3 = OAc$

^1H NMR Examination. Summarized in Table I are the pertinent ^1H NMR data for compounds **2a–e** and **3a–e**, as well as the chemical shift values which we found for 6β-naloxol 3,6,14-triacetate (**5b**) and 6α-naloxol 3,6,14-triacetate (**6b**).

Table I. Pertinent ^{1}H NMR Chemical Shifts of 6β-Naltrexol, 6α-Naltrexol, and Their Respective Acetate Derivatives[a]

Compd	Acetate methyls			5β-H	6α-H	6β-H	$J_{5\beta\text{-}6}$[b]
	3	6	14				
2a				4.53 (d)	3.54 (m)		6.0
2b	2.26 (s)			4.51 (d)	3.53 (m)		6.0
2c		2.06 (s)		4.60 (m)			Nm
2d	2.25 (s)	2.07 (s)		4.64 (m)			Nm
2e[c]	2.26 (s)	2.07 (s)	2.14 (s)	4.63 (m)			Nm
5b[c]	2.25 (s)	2.07 (s)	2.12 (s)	4.64 (m)			Nm
7d[d]		2.07 (s)		4.43 (d)	4.5		6.5
3a				4.64 (d)		4.26 (m)	4.0
3b	2.27 (s)			4.63 (d)		4.14 (m)	5.2
3c			2.07 (s)	4.66 (d)		4.15 (m)	4.0
3d	2.28 (s)	1.90 (s)		4.78 (d)		5.40 (m)	5.0
3e[c]	2.27 (s)	1.94 (s)	2.13 (s)	4.80 (d)		5.30 (m)	5.0
6b[c]	2.27 (s)	1.94 (s)	2.10 (s)	4.78 (d)		5.2 (m)[e]	5.0
8[d]		1.81 (s)		4.59 (d)		5.2	5.7

[a] All experimental chemical shifts were obtained in $CDCl_3$ solution and are expressed in parts per million downfield from tetramethylsilane. Multiplicities are denoted by s (singlet), d (doublet), and m (multiplet). [b] Coupling constants are in cycles per second. Those cases in which the coupling constants were not measured are denoted by nm. [c] In the 3,6,14-triacetates the 9α-H appeared as a downfield doublet. The chemical shifts were 4.42 (**2e**), 4.26 (**5b**), 4.48 (**3e**), and 4.29 (**6b**). [d] Values are from ref 18. [e] The 6β proton was part of a three-proton multiplet that included two of the olefinic protons.

Also included in Table I are the corresponding literature values for 6-acetoxy-7,8-dihydroisocodeine (**7**) and 6-acetoxy-7,8-dihydrocodeine (**8**).[18]

The chemical shifts of the 5β and 6 protons of **2a** and **3a** were in excellent agreement with previously reported values.[5,7] In addition, the methyl chemical shifts of the 3,6,14-triacetates **2e** and **3e** (and hence **5b** and **6b**), which were unequivocally assigned by comparison with the respective mono- and diacetate values, agreed well with the chemical shifts found by Malspeis and co-workers.[7] The characteristic upfield shift of the 6-acetoxyl methyl in the 6α series, due to the increased shielding effect of the aromatic ring,[7,18] was clearly observed. The good agreement of the observed 6-acetoxyl methyl chemical shifts with those of compounds **7** and **8** provided strong evidence for the chair conformation of ring C in both the 6β and 6α series.

From the data in Table I it was apparent that acetylation of the 6-hydroxyl group of **2a** or **3a** consistently deshielded the corresponding 6 proton. The resultant downfield shift of approximately 1.1 ppm was of the magnitude expected for a secondary alcohol.[19] In contrast, Hahn and Fishman concluded from their ^{1}H NMR data that the 6-hydroxyl group of 6β-naloxol (**5a**) and 6α-naloxol (**6a**) could be acetylated without effecting any downfield shift of the proton.[11] However, our results with the 3,6,14-triacetates **5b** and **6b** closely paralleled those obtained for compounds **2e** and **3e**, as expected.[20]

In a previous ^{1}H NMR study on the morphine alkaloids, Okuda and co-workers[18] showed that the magnitude of $J_{5\beta\text{-}6}$ often yielded valuable information about the conformation of ring C. For compounds **2a** and **2b** the $J_{5\beta\text{-}6}$ value was in good agreement with the theoretical value[18,21] for the chair conformation. However, a complete analysis in the 6β series was impractical because acetylation of the 6-hydroxyl group caused the 5β and 6α protons to appear as a two-proton multiplet. In the 6α series the $J_{5\beta\text{-}6}$ value yielded conflicting information about the conformation of ring C. This was due partially to the qualitative nature and narrow range of the theoretical values,[18,21] and partially to intramolecular hydrogen bonding (vide infra).

^{13}C NMR Examination. The ^{13}C NMR chemical shifts for each series of compounds are given in Table II. The assignment of the ^{13}C resonances of 6β-naltrexol (**2a**) and 6α-naltrexol (**3a**) was described earlier, as were the procedures used to assign the ^{13}C resonances in the spectra of the corresponding acetates.[10]

The upfield shift of the C-6 resonance in going from **2a** to **3a** was clearly indicative of going from an equatorial to an axial alcohol[22] and was consistent with the chair conformation of ring C in these compounds. Moreover, the upfield positions of the C-5, C-7, and C-8 signals in the spectrum of **3a** reflected respectively the smaller β effect and the larger γ effect of the axial 6-hydroxyl group. Rerunning the spectra of **2a** and **3a** in dimethyl sulfoxide-d_6 solution produced only minor solvent effects on the chemical shift values.

The ^{13}C NMR spectra of the various 6β-naltrexol acetates were also consistent with a ring C chair conformation. As expected, acetylation of the phenolic hydroxyl group (compound **2b**) produced only changes in the aromatic chemical shifts. Acetylation of the 6-hydroxyl group (compound **2c**) caused a downfield shift of 3 ppm in the C-6 resonance and an upfield shift of 2–3 ppm in the C-5 and C-7 signals. These effects were again typical of an equatorial alcohol.[23] Acetylation of the 14-hydroxyl group (compound **2e**) produced the expected downfield shift of the C-14 signal[24] and a 5–7 ppm upfield move of the C-8 and C-9 resonances due to the γ effect of the axial 14-acetoxyl group.

The situation in the 6α-naltrexol series was slightly more complex. That acetylation of the phenolic hydroxyl group of **3a** affected the shape of ring C was suggested by the change in $J_{5\beta\text{-}6}$ in the ^{1}H NMR (vide supra). In addition to the expected changes in the aromatic resonances, the ^{13}C NMR spectrum of compound **3b** in deuteriochloroform solution showed an 0.83 ppm downfield shift for the C-7 resonance and a 2.45 ppm upfield shift for the C-8 signal. However, in dimethyl sulfoxide-d_6 solution the C-7 and C-8 signals showed no change due to acetylation. These observations suggested the existence of an intramolecular hydrogen bond between the axial 6-hydroxyl group and the 3-acetoxyl group which was disrupted in dimethyl sulfoxide-d_6 solution. The effect of the hydrogen bond was to distort ring C so that C-8 experienced increased shielding by the axial C-6 substituent.

The intramolecular hydrogen bonding observed in compound **3b** was possible only with ring C in the chair conformation. Moreover, the existence of the hydrogen bond undoubtedly contributed to the decreased reactivity of the axial 6-hydroxyl group toward derivatization with acetic anhydride or pentafluoropropionic anhydride.[25] In addition, the facile conversion of 3,6-diacetate **3d** to 6α-naltrexol (**3a**) was no doubt due to neighboring-group effects made possible by the close proximity of the 3- and 6-acetoxyl groups.

Acetylation of the 6-hydroxyl group of **3a** (compound **3d**)

Table II. Carbon-13 Chemical Shifts of 6β-Naltrexol, 6α-Naltrexol, and Their Respective Acetate Derivatives[a,b,c]

Carbon	2a	2b	2c	2d	2e	3a	3b[d]	3c	3d	3e
1	118.89	118.56	119.10	118.61	118.90	118.94	118.61	118.95	118.22	118.51
2	117.53	122.07	117.15	122.40	122.61	117.63	121.39	117.59	122.01	122.56
3	139.81	132.95	139.58	133.32	133.58	137.37	132.90	136.92	131.53	131.53[b]
4	142.30	147.00	141.87	146.09	146.26	145.57	148.31	144.93	149.00	149.34
5	95.78	96.27	92.66	92.39	92.22	90.51	91.49	90.26	87.88	87.69
6	72.62	71.79	75.59	75.35	74.91	66.77	66.42	66.62	68.22	67.89
7	26.00	25.12	23.31	23.22[c]	22.97[b]	22.97	23.80	23.46[c]	21.27	22.38
8	30.54	30.82	30.33	29.96[b]	24.97	28.64	26.19	25.69	27.24	23.80
9	62.14	61.79	62.08	61.91	55.45	61.94	62.13	55.79	62.05	55.50
10	22.63	22.82	22.53	23.22[c]	23.31[b]	22.69	22.92	23.46[c]	23.26	23.46[b]
11	123.72	130.46	124.32	129.29	131.00[b]	125.23	130.70[b]	126.04	131.04[b]	131.24[b]
12	131.38	132.51	131.10	131.58	131.10[b]	130.84	131.19[b]	129.49	130.31[b]	130.51
13	47.26	46.87	47.89	47.49	48.09	47.26	46.09	47.98	46.96	47.55
14	70.38	69.89	69.89	69.77	82.13	69.89	69.89	81.81	69.68	81.79
15	29.56	29.02	29.55	29.43[b]	29.55	33.22	31.89	33.22	32.25	31.99
16	43.90	43.45	43.79	44.19	43.94	43.07	43.40	43.56	43.61	43.50
17	59.06	59.06	59.06	59.00	59.11	59.40	59.16	59.63	59.34	59.40
3 CH_3CO		168.50		167.70	168.06		168.70		167.99	168.31
3 CH_3CO		20.58		20.89	20.58		20.53		20.84[b]	20.53[b,c]
6 CH_3CO			170.70	169.83	170.11[c]				169.69	170.16[c]
6 CH_3CO			21.26	21.38	21.12[b]				21.03[b]	20.53[b,c]
14 CH_3CO					170.11[c]			169.73		170.16[c]
14 CH_3CO					22.19[b]			22.73		20.78[b]
	9.23	9.12	9.26	9.04	9.26	9.18	9.17	9.52	9.38	9.22
	3.91[c]	3.75 3.66	3.85[c]	4.38 4.04	3.66[c]	3.82 3.62	3.80 3.66	4.14 3.89	4.09[c]	3.75 3.61

[a] Chemical shifts were obtained in $CDCl_3$ and are expressed in parts per million downfield from tetramethylsilane. [b] Signals in any one column may be reversed. [c] These resonances were twice as intense as other similar resonances. [d] In Me_2SO-d_6 the resonance for C-6 appeared at 65.26, C-7 at 22.93, C-8 at 28.10, and C-15 at 32.83.

produced a 1.4-ppm upfield shift of the C-8 resonance due to the larger γ effect of the axial 6-acetoxyl group. Acetylation of the 14-hydroxyl group (compounds **3c** and **3e**) caused the expected shifts of the C-8, C-9, and C-14 signals. In the 6α-naltrexol series the upfield shift of the C-8 resonance due to the 14-acetoxyl group was not as great as that in the 6β-naltrexol series.

An interesting difference between the two series of compounds was the appearance of the C-15 resonance at 2–4 ppm lower field in the 6α-naltrexol series. This difference was greatest for the parent compounds (**2a** and **3a**), was independent of solvent (except for compound **3b**), and was only slightly affected by acetylation. In addition, the C-3 and C-4 signals appeared respectively 1–2 ppm further upfield and 2–3 ppm further downfield in the 6α-naltrexol series. However, these changes were not as prominent as the shift of the C-15 resonance.

An examination of space-filling models indicated that the 6 substituent is more crowded by the ether oxygen and the aromatic ring in the α configuration than in the β configuration. One effect of this crowding could be the distortion of the carbon and oxygen substituents that are β and γ to C-15, thereby affecting the β and γ interaction between these atoms. The 6 substituent is also δ to both C-15 and C-4 (via the ether bridge). Although a δ interaction[26–28] could explain the shift of the C-4 resonance, the geometry between C-15 and the 6 substituent in either configuration is wrong for a δ interaction of much magnitude.[26,28] We are hopeful that the relationship between the chemical shift of C-15 and the configuration of C-6 will become clear upon examination of the ^{13}C NMR spectra of other ring C saturated compounds.

Experimental Section

NMR Spectral Measurements. ^1H NMR spectra were recorded in $CDCl_3$ solution on a Varian HA-100 spectrometer. ^{13}C NMR spectra were determined at 25.03 MHz on JEOL JNM-PS-100 FT NMR spectrometer interfaced with a Nicolet 1085 Fourier transform computer system under conditions previously described.[10] A 45° pulse of 12.5 μs was used, and the noise-modulated proton decoupling covered a bandwidth of 2500 Hz.

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Registry No.—**2a,** 49625-89-0; **2b,** 59888-59-4; **2c,** 59888-60-7; **2d,** 59888-61-8; **2e,** 59906-25-1; **3a,** 20410-98-4; **3b,** 59888-62-9; **3c,** 59888-63-0; **3d,** 59888-64-1; **3e,** 59888-65-2; **5b,** 53154-17-9; **6b,** 53154-16-8.

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Carbanions. 2.[1] Carbon-13 Nuclear Magnetic Resonance Study of Meisenheimer Complexes and Their Charge Distribution Pattern

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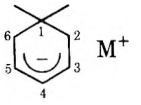
A series of 6-X,2,4-dinitroanisoles and their carbanionic methoxide addition products (Meisenheimer complexes) have been examined by ^{13}C NMR spectroscopy. Variation of X (CF_3, H, Cl, F, CH_3) does not affect the charge distribution pattern in the complexes as reflected by their ^{13}C NMR shifts. Only in the case where X is NO_2 can a change be observed. The ^{13}C NMR studies indicate that the cyclohexadienylic carbons carry about 0.3–0.4 e more negative charge than the corresponding carbons in their aromatic precursors. The additional charge is located on C_2, C_4, and C_6.

Intensive studies on the interaction of electron-deficient aromatic compounds with alkoxides culminated in 1902 with Meisenheimer's evidence that these complexes could be described by the structural formula **1**.[2] These complexes, however, attracted little attention until 1964 when Crampton and Gold reported the first ^{1}H NMR spectrum of a Meisenheimer complex.[3a] Since then, numerous papers on the ^{1}H NMR studies of these complexes have been published,[3b] some of which also discussed aspects of their charge distribution pattern.[4] However, electron-withdrawing groups must occupy at least two and often three of the positions ortho and para (i.e., 2, 4, and 6) to the aliphatic center 1 in order to obtain stable complexes. As a result, the ortho and para positions, which are expected to carry most of the negative charge in cyclohexadienyl anions, cannot be studied by ^{1}H NMR spectroscopy, and the limitations of the ^{1}H NMR method of investigating charge distributions become evident.



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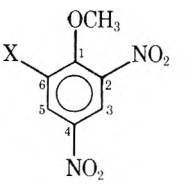
We now wish to report the first ^{13}C NMR spectroscopic study of Meisenheimer complexes, in which the obvious limitations of the ^{1}H NMR method are absent.

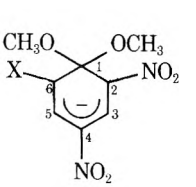
Results[5]

Substituted Anisoles. All ^{13}C NMR spectra showed a high-field absorption close to δ_C 65 (Table I), which was assigned to the methoxyl carbon based on the chemical shift and its quartet splitting in off-resonance spectra. Furthermore, off-resonance experiments allowed the separation of the C_3 and C_5 shifts from the other carbon shifts. δ C_3 and C_5 were found to be identical in anisoles **2** and **3**. In **6** these carbon shifts were characterized on the basis of the C–F couplings (J_{C_5F} = 14, J_{C_3F} = 8 Hz). In all other cases C_3 and C_5 were separated by more than 10 ppm, and their assignments were made possible by comparison of the observed shifts with calculated shifts.[6] The observed shifts showed a maximum deviation of 3.1 ppm from those which were determined from the substituent increments in monosubstituted benzenes.[6]

In accord with the calculations the most deshielded peaks were always ascribed to C_1. The only exception was **6** where C_6 was most deshielded, as indicated by the calculations and experimentally proved by its CF coupling of 231 Hz. The resonance at δ_C 127.6 was the only sp^2 carbon absorption of **3** showing CF coupling (6 Hz) and therefore could be assigned to C_6. Though the similarity between the calculated and observed C_1 and C_6 shifts in **5** and **7** is not outstanding, comparison with the resonances of the other singlets shows that no other assignment is possible.

In general, the nitro-substituted positions C_2 and C_4 show only slightly different chemical shifts. Though their assignments were not crucial to our present study, it was attempted on the basis of their intensities. If C_6, C_2, and C_4 in **2** had the





X		
NO_2	**2**	**2a**
CF_3	**3**	**3a**
H	**4**	**4a**
Cl	**5**	**5a**
F	**6**	**6a**
CH_3	**7**	**7a**

Table I. ^{13}C NMR Shifts of 2,4-Dinitro-6-X-anisoles at 15.1 MHz in $CDCl_3$ with Me_4Si as External Standard, Calculated Shifts[6] in Parentheses

Compd[a]	X	C_1	C_2	C_3	C_4	C_5	C_6	OCH_3	Other
2	NO_2	153.1	145.6	125.3	142.5	125.3	145.6	66.4	
		(156.1)	(135.9)	(125.7)	(142.6)	(125.7)	(135.9)		
3	CF_3	158.1	144.1	126.2	142.6	126.2	127.6	65.4	122.5
		(158.7)	(135.3)	(123.1)	(142.0)	(128.3)	(114.9)		(J = 274 Hz)
4	H	158.5	139.5	122.6	141.7	130.4	115.2	58.7	
		(160.9)	(135.0)	(119.9)	(141.7)	(130.5)	(106.9)		
5	Cl	155.8	145.4	120.3	143.4	130.2	132.6	64.2	
		(161.3)	(136.3)	(118.0)	(143.0)	(130.9)	(122.1)		
6	F	147.3	141.8	117.0	144.1	117.9	156.2	64.0	
		(148.0)	(136.4)	(115.4)	(143.1)	(117.6)	(150.7)		
7	CH_3	157.5	144.0	119.7	143.1	130.5	137.6	63.4	17.5
		(161.6)	(134.9)	(117.0)	(141.6)	(131.2)	(124.8)		

[a] Respective registry numbers are 606-35-9, 320-16-1, 119-27-7, 23789-10-8, 344-78-5, 29027-13-2.

Table II. ^{13}C NMR Shifts of 1,1-Dimethoxy-2,4-dinitro-6-X-cyclohexadienyl Anions at 25.16 MHz in Me_2SO-d_6 with Me_4Si as External Standard[a]

Compd[b]	X	C_1	C_2	C_3	C_4	C_5	C_6	OCH_3	Other
2a	NO_2	104.3 (s)	129.2 (s)	131.2 (d)	119.3 (s)	131.2 (d)	129.2 (s)	53.2 (q)	
	NO_2[c]	103.9	129.2	130.0	118.8	130.0	129.2	52.8	
3a	CF_3	104.8 (s)	123.5 (s)[d]	131.8 (d)	119.8 (s)[d]	129.7 (dq)	111.3 (q)	52.6 (q)	125.7 (q)
4a	H	104.1 (s)	122.9 (s)	131.1 (d)	121.7 (s)	125.4 (d)	118.5 (d)	52.0 (q)	
5a	Cl	104.9 (s)	121.2 (s)[d]	130.5 (d)	120.6 (s)[d]	126.0 (d)	120.7 (s)[d]	52.5 (q)	
6a	F	103.7 (d)	121.2 (d)	128.8 (d)	118.4 (d)	107.8 (dd)	148.3 (d)	52.8 (q)	
7a	CH_3	106.0 (s)	120.7 (s)	130.9 (d)	122.6 (s)	123.9 (d)	125.4 (s)	52.0 (q)	16.7 (q)

[a] Multiplicities refer to one-bond CH couplings and all fluorine couplings. [b] Respective registry numbers are 12128-30-2, 33516-46-0; 12128-33-5, 25230-80-2, 33542-12-0, 59906-98-8. [c] 1:1 complex with 18-crown-6 ether dissolved in THF. [d] Assignments uncertain; see text.

same relaxation time, a 2:1 intensity ratio should have been observed. We detected, however, two signals of equal intensity and concluded that C_4 was relaxing faster. Using a lower pulse width resulted in an increase of intensity of the δ_C 145.6 peak relative to that at δ_C 142.5 and the latter was identified as C_4. Generalizing this observation to the anisoles **3**–**7** we ascribed the less intensive resonance of the nitro-substituted carbons to C_2.

Meisenheimer Complexes. All spectra were characterized by a quartet absorption around δ_C 52 and a singlet around δ_C 104, which were assigned to the methoxy carbon and C_1, respectively (Table II).

The trinitro compound **2a** with C_{2v} symmetry showed a doublet at δ_C 131.2 (C_3, C_5) and two singlets at δ_C 129.2 (C_2, C_6) and 119.3 (C_4), which could be assigned due to their 2:1 ratio of intensities.

In **3a** the quartet at δ_C 111.3 (J_{CF} = 27.6 Hz) was ascribed to C_6. A smaller CF coupling (J_{CF} = 6 Hz) was also detected in the signal at δ_C 129.7 which, in addition to the off-resonance experiments, allowed attribution to C_5. While the off-resonance splitting of the δ_C 131.8 resonance also revealed C_3, the assignment of C_2 and C_4 was not directly possible. As shown below, the C_4 shift was found to be almost constant in all systems. Therefore, C_4 was tentatively ascribed to the resonance at δ_C 119.8 and C_2 to that at δ_C 123.5.

4a showed three carbons attached to hydrogen at δ_C 118.5, 125.4, and 131.1; the highest field signal was attributed to C_6. A trace of CH_3O^-, added to the solution of **4a** in Me_2SO-d_6, caused a slow decrease of the signal at δ_C 131.1 while all other peaks remained unchanged. This observation was interpreted as an exchange of 3-H by deuterium.[7] The fact that no change in the NMR spectrum was observed in Me_2SO/CH_3O^- solution emphasizes the above explanation. The doublets at δ_C 125.4 and 131.1, therefore, could be assigned to C_5 and C_3, respectively. In the proton-coupled spectra the signal at δ_C 122.9 was split into a doublet and was assigned to C_2, since a different splitting pattern had to be expected for C_4. The observation of the proton coupled C_4 was not possible because its signal overlapped with C_6 and C_5.

The three singlets assigned to C_2, C_4, and C_6 of **5a** were in such close proximity that they could not be ascribed specifically. Since the C_3 shielding is relatively constant in all systems, it was assigned to the doublet at δ_C 130.5 and the remaining doublet at δ_C 126.0 to C_5.

In **6a** the signal at δ_C 128.8 was the only ring carbon that did not show fluorine coupling and therefore was assigned to C_3. C_6 was coupled to fluorine with a coupling constant of 258 Hz while C_1 and C_5 displayed coupling constants of 23 Hz. Since the signals of C_2 and C_4 were doublets with the same CF coupling constant of 11 Hz, the proton-coupled carbon spectrum was necessary for their assignments. The resonance at δ_C 121.2 was then split by one hydrogen (J_{CH} = 4 Hz) and assigned to C_2 while the resonance at δ_C 118.4 was coupled to two hydrogens (J_{CH} = 4 Hz) and assigned to C_4.

In **7a** long distance couplings allowed the assignment of the resonances at δ_C 123.9 and 130.9 to C_5 and C_3, respectively. The C_3 resonance at δ_C 130.9 was split by its adjacent hydrogen with a coupling of 164 Hz, and by H_5 with a coupling constant of 4 Hz. In addition to the corresponding couplings, C_5 was also split by the methyl group resulting in a pair of quintets, one of which coincided with C_2. In the coupled spectrum the resonance at δ_C 125.4 appeared as a distorted quintet in which both CH_3 and H_5 were coupled similarly to C_6. Finally the doublet of 5 Hz at δ_C 120.7 was ascribed to C_2. The expected triplet splitting of C_4 by H_3 and H_5 was only observed as a broad line.

Discussion

Substituted Anisoles. Table I shows an excellent agreement between calculated and observed shifts of the positions C_3, C_4, and C_5. Since the maximum deviation found is 3.1 ppm, the additivity of the substituent effects[6] is well demonstrated. In the case of C_1 the maximum deviation becomes 5.5 ppm. The correspondence between the calculated and observed

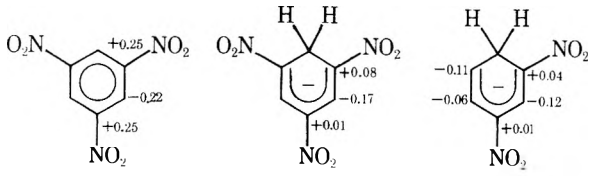


Figure 1. Calculated π-electron charges.[9]

shifts, however, is poor for C_2 and C_6. A difference of 10 ppm is frequently observed. Since C_6 as well as C_2 are more deshielded than expected from the calculations, the reason might be the steric inhibition of resonance of the methoxyl group.

This is stressed by the fact that the calculated and observed values agree very well in the case of the hydrogen substituted compound **4**, in which a planar conformation of the methoxyl group can be achieved. On the other hand, it is not clear why the agreement is so close for C_4, as the distorted coplanarity of the methoxyl group should also affect that position.

Meisenheimer Complexes. In structurally similar molecules a linear correlation between ^{13}C NMR shifts and charge densities can be expected, particularly if relatively small charges are considered.[8] In the complexes **2a–7a**, therefore, the chemical shifts of C_2, C_3, and C_4 should reflect the relative electron density as they are separated from the substituent X by three or four bonds.

MO and resonance theory predict that C_3 will not carry any significant charge in cyclohexadienyl ions and the constancy of this shift (Table II) thus is not surprising. On the other hand the C_4 shielding also remains unchanged while C_2 experiences a deshielding as the electron-withdrawing ability of X increases. These results support SCF MO calculations by Wennerström[9] (Figure 1). While a π-electron charge of +0.01 was calculated for C_4 of both the 2,4-dinitrocyclohexadienyl anion and the 2,4,6-trinitrocyclohexadienyl anion, the positive charge of +0.08 at C_2 of the trinitrocyclohexadienyl anion decreases to +0.04 in the dinitro compound. The difference of 0.04 ppm corresponds to 6.4 ppm if the slope of the correlation line is accepted to be 160 ppm per electron charge.[8] The coincidence of this value with the observed difference between the C_2 resonances of **2a** and **4a** is regarded to be accidental.

Data of Table II furthermore show that, disregarding a small effect of CF_3, only NO_2 exerts a considerable deshielding of C_2. The ^{13}C NMR data, therefore, demonstrate that NO_2 stabilizes the negative charge much better than CF_3. This conclusion is supported by the fact that neither 2-methoxy-5-nitrobenzotrifluoride nor 4-methoxy-3-nitrobenzotrifluoride show a color change when treated with $^-OCH_3$ (indicative of formation of Meisenheimer complex), while 2,4-dinitroanisole (**4**) yielded the crystalline complex **4a**.

To ascertain that the observed chemical shifts of the anions are not influenced by a significant ion pairing effect,[10] the ^{13}C NMR spectrum of **3a** was also recorded in the presence of 18-crown-6 ether. Table II shows that the deviations are less than 1.2 ppm and can be thus neglected.

Comparison between Meisenheimer Complexes and Their Precursors. HMO calculation led to the conclusion that the addition of alkoxides to polynitrobenzenes causes a decrease of negative charge on the ring carbons.[11] Because this conclusion contradicted more elaborate quantum mechanical calculations,[9,12] we compared the ^{13}C shifts of the studied Meisenheimer complexes with their precursors (Table III).

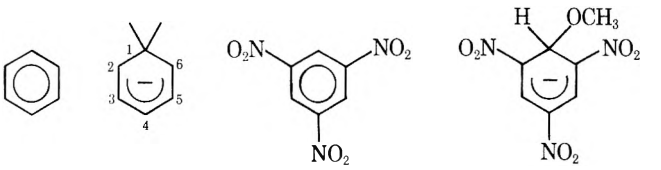
First it is necessary to evaluate the importance of factors other than charge densities that might influence the chemical shifts.

Comparing the shieldings of the sp^2 carbons in benzene, 1,3-cyclohexadiene, and cyclohexene,[13] it becomes obvious that the replacement of a CH group in benzene by CH_2 does not significantly affect the shifts of the other olefinic carbons.

Table III. Differences between the ^{13}C NMR Shifts of the Meisenheimer Complexes 2a–7a and the Anisoles 2–7

X	C_2	C_3	C_4	C_5	C_6	Sum
NO_2	−16.4	+5.9	−23.2	+5.9	−16.4	−44.2
CF_3	−20.6	+5.6	−22.8	+3.5	−16.3	−50.6
H	−16.6	+8.5	−20.0	−5.0	+3.2	−29.9
Cl	−24.2	+10.2	−22.8	−4.2	−11.9	−52.9
F	−20.6	+11.8	−25.7	−10.1	−7.9	−52.5
CH_3	−23.3	+11.2	−20.5	−6.6	−12.2	−51.4

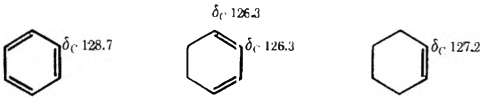
Table IV. ^{13}C NMR Shifts of the Compounds 8, 8a, 9, and 9a



8 8a 9 9a

	C_2	C_3	C_4	C_5	C_6	Sum
8[a]	128.7	128.7	128.7	128.7	128.7	
8a[b]	75.8	131.8	78.0	131.8	75.8	
Δ(8a/8)	−52.9	+3.1	−50.7	+3.1	−52.9	−150.3
9[c]	149.5	125.2	149.5	125.2	149.5	
9a[d]	132.6	127.0	122.2	127.0	132.6	
Δ(9a/9)	−16.9	+1.8	−27.3	+1.8	−16.9	−57.5

[a] Reference 13, p 95. [b] In NH_3 at −70 °C. [c] In $CDCl_3$. [d] In Me_2SO/CH_3OH.



Therefore, it is concluded that the change in carbon shifts between benzene and the cyclohexadienyl anion is almost entirely due to charge effects (Table IV). In fact, the observed shielding of 150 ppm is very close to that predicted by the Spiesecke–Schneider relationship for the shielding of aromatic carbons by one electron (160 ppm).[8]

The comparison of **2a** with **9a** furthermore shows that the replacement of OCH_3 by H at C_1 results in a deshielding for C_2, C_6 (+3.4 ppm), and C_4 (+2.9 ppm) and a shielding for C_3 and C_5 (−4.2 ppm). These effects sum up to 1.3 ppm for all carbons C_2 to C_6 and can be thus neglected. Consequently it is possible to compare the total shieldings of the olefinic carbons in different cyclohexadienyl anions irregardless of their substitution at C_1 by H or OCH_3.

In contrast to the 150-ppm shielding which accompanies the formation of the cyclohexadienyl anion from benzene,[14] the addition of methoxide to trinitrobenzene results in an additional shielding of only 57 ppm. Since it is improbable that the approximations made during this derivation influence this large difference significantly, we can conclude that the electron density of the olefinic carbons in **9a** is increased by ~0.4 e relative to the precursor **9**, while ~0.6 e is absorbed by the nitro groups. This value is similar to the 0.48 e increase of negative ring charge predicted by SCF MO calculations (Figure 1). On the other hand, the inability of the HMO method[11] to treat problems of this kind is demonstrated.

The formation of the σ complexes from **5**, **6**, and **7** results in an additional shielding of 52 ppm (Table III). Almost the same result is observed in the CF_3 system and a noteworthy difference is found only for the trinitro compound **2** (44 ppm). The smaller increase of electron density on the carbon atoms of **2a** again demonstrates the exceptional ability of NO_2 to attract electrons. As discussed earlier, the electron density

released by the coplanar methoxyl group is more effective in dinitroanisole (**4**) than in the other trisubstituted anisoles **3–7**. Since the mesomeric effect of the OCH_3 group is lost in the σ complexes, the relatively small increase of shielding from **4** to **4a** can be explained.

The difference between the pairs **2/2a** (44 ppm) and **9/9a** (57 ppm) can be interpreted analogously. While the average shifts of the complexes **2a** and **9a** are identical, the carbons 2–6 carry more negative charge in the trinitroanisole **2** than in trinitrobenzene **9**, in which the electron-releasing OCH_3 group is missing.

Disregarding **4** because of its special properties, the data of Table III reveal some other systematic trends. It is obvious that in all systems, C_2 and C_4 and to a minor degree also C_6 experience the increase of electron density as a consequence of the added methoxide ion forming the Meisenheimer complex. The deshielding which is observed for C_3 is also reflected by SCF MO calculations (Figure 1). The effects in C_5 are not yet clearly understood.

Conclusion

In 6-X,2,4-dinitrocyclohexadienyl anions (X = CH_3, Cl, F, H, CF_3) the variation of substituent X has almost no effect on the overall charge distribution. Only in the case of X = NO_2 is a difference observed, demonstrating the superior ability of the NO_2 group in stabilizing negative charge.

The ^{13}C NMR data do not allow a conclusion about the absolute charge distribution in anionic σ complexes. They do demonstrate, however, that the cyclohexadienylic carbons carry about 0.3–0.4 e more negative charge than the corresponding positions in their aromatic precursors. The additional charge is located on C_2, C_4, and C_6, while the other positions remain unchanged or even experience a small deshielding effect.

Experimental Section

Anisoles. Trinitroanisole (**2**) and 2-methoxy-3,5-dinitrobenzotrifluoride (**3**)[15] (bp 128–130 °C, 0.25 Torr) were readily prepared in the usual manner by treating picryl chloride and 2-chloro-3,5-dinitrobenzotrifluoride with $NaOCH_3$. The anisoles **5**[16] (bp 128–131 °C, 0.05 Torr), **6**[17] (bp 118–120 °C, 0.025 Torr), and **7**[18] (mp 68–70 °C) were prepared by nitration of the O-substituted anisoles according to literature procedures. All other compounds were commercially available.

Preparation of Meisenheimer Complexes. 2a–7a were prepared as crystalline compounds in analogy to the procedure described for the preparation of **4a**.[4c] In contrast to the other complexes **2a–7a**, **4a** was not stable in Me_2SO solution. However, addition of a trace of CH_3O^-/CH_3OH to the Me_2SO stabilized the ion and allowed its NMR spectra to be obtained. A stable solution of **9a** was prepared by adding a solution of $KOCH_3$ (2.1 mmol) in CH_3OH to trinitrobenzene (2.0 mmol) dissolved in Me_2SO. Addition of 18-crown-6 ether to a solution of **2a** in Me_2SO yielded a crystalline precipitate, identified as a 1:1 complex of **2a** and 18-crown-6 ether by integration of its ^1H NMR spectrum. Since the solubility of the complex in Me_2SO was bad, it was dissolved in tetrahydrofuran for the examination of the NMR spectra. The reaction of 1,4-cyclohexadiene with KNH_2 in NH_3 at −78 °C yielded a solution of the cyclohexadienyl anion, contaminated by a trace of benzene.[19] The solution was stable at −70 °C, at which temperature the spectrum was taken.

Carbon-13 Magnetic Resonance Spectra. The spectrometers used were Varian Associates Model XL-100 and a modified HA-60 equipped with a broad-band decoupler and a variable temperature probe.

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Registry No.—**8**, 110-82-7; **8a**, 27900-34-1; **9**, 99-35-4; **9a**, 12244-65-4.

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Isomerization Studies. 4. Isomerization of Acyl Halides in the Presence of Palladium Catalysts

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The direct catalytic isomerization of acyl halides to their α-branched isomeric counterparts has been studied. For example, when nonanoyl chloride is heated at 150 °C in the presence of $PdBr_2$ catalyst, a mixture of 2-methyloctyl, 2-ethylheptyl, and 2-propylhexyl acyl chlorides is obtained. Reaction parameters are very critical in determining the nature and type of products obtained from this isomerization process. At reaction temperatures up to 220 °C, other products obtained from the reaction in varying amounts are either a monoene or alkyl halide having one less carbon atom than the starting acyl halide. The addition of a phosphine ligand to the catalyst system or the introduction of unsaturation in the acyl halide results in a suppression of the isomerization reaction.

The decarbonylationn of acid halides and aldehydes with transition metal catalysts has been demonstrated to be a synthetically useful reaction.[2] When acid chlorides with no β-hydrogen atoms are decarbonylated, alkyl chlorides are the major products, whereas when acid chlorides containing a β-hydrogen atom are decarbonylated, olefins are the primary products.[2,3] Higher aliphatic acyl chlorides and bromides are decarbonylated in high yields when they are heated above 200 °C in the presence of a catalytic amount of selected palladium catalysts.[4,5] On the other hand, the carbonylation of olefins to acids or esters has been accomplished with these same palladium catalysts when the reactions are performed in the presence of hydrogen halides. Accordingly, the mechanism of both the carbonylation and decarbonylation reactions with palladium catalysts have been postulated to proceed via the same pathway.[4] In view of the foregoing, it seemed plausible that under the proper reaction conditions a palladium catalyst might effect the decarbonylation–carbonylation of acid chlorides in one step. One result of such a reaction, which may have synthetic utility, would be the conversion of a normal chain acid chloride into an isomeric α-branched chain counterpart or vice versa. It is the purpose of this report to describe the development of a catalyst system which does achieve such a skeletal isomerization.

As previously noted,[4,5] acyl halides containing an available β-hydrogen atom, when heated in the presence of selected transition metal catalysts, readily undergo decarbonylation–dehydrohalogenation to a monoene, having one less carbon atom than the starting acyl chloride. Carbon monoxide and hydrogen chloride are also produced. For example, heating palmitoyl chloride at 220 °C in an open flask in the presence of palladium acetylacetonate (expt 1, Table I) resulted in the quantitative formation of pentadecene. As reported for stearoyl chloride,[5] the olefin formed had its double bond randomly distributed within the internal positions of the hydrocarbon chain with no indication of branching of the hydrocarbon backbone. In contrast to the above, when the decarbonylation of palmitoyl chloride was carried out in a sealed reactor under similar reaction conditions (Table I) decarbonylation was incomplete, and the product mixture was more complex. Treatment of the latter mixture with methanol gave the expected pentadecene and residual methyl palmitate and two additional groups of products. One group was identified as being a mixture of secondary C_{15} alkyl chlorides, whereas the other was identified as a mixture of isomeric α-branched C_{16} methyl esters. Alkyl chloride formation is probably the result of the addition of hydrogen chloride to the first formed product, pentadecene, since with an increase in reaction time the amounts of both alkyl chloride and alkene increased (expt 2 and 3, Table I). On the other hand, lowering the reaction temperature to 150 °C resulted in an increased yield of isomeric C_{16} acid chlorides and eliminated alkyl chloride formation (expt 4, Table I). A similar result was obtained when the identical reaction was carried out in an open flask at 150 °C, rather than a sealed reactor (expt 5, Table I). Therefore, we concluded that the formation of α-branched acid chlorides from normal chain isomers was a result of a skeletal isomerization process and not a carbonylation reaction and that a sealed system was not required to achieve such a transformation.

In view of the above, a more extensive examination of this isomerization reaction as regards to catalyst composition, acid chloride structure, and reaction temperature and time was undertaken. The objective of this phase of the study was to determine the optimum conditions for the isomerization of normal chain acid chlorides into their isomeric α-branched chain counterparts and at the same time to avoid formation of decarbonylation products.

Catalyst composition was studied first. Changing the palladium catalyst ligand from acetylacetonate to chloride ion and heating at 150 °C for 5 h resulted in an undesirable increase in yield of pentadecene from palmitoyl chloride; compare expt 5 to 6, Table I. This result was in agreement with previous data which showed that palladium chloride is a very efficient decarbonylation catalyst.[4] In contrast, palladium bromide catalyst gave less alkene formation and more isomerized acyl halide (expt 7, Table I). Even better yields of isomerized acid halides were obtained with the palladium bromide catalyst when the reaction was carried out at 130 °C (expt 8, Table I) instead of 150 °C.

Heating pelargonyl chloride with palladium bromide at 150 °C resulted in extensive decarbonylation (>60%) to C_8 alkene, whereas at 130 °C alkene formation was negligible compared to acid chloride isomerization (expt 9, Table I). Prolonging the reaction time to 18 h increased the amount of α-branched acid chlorides but also increased the amount of alkene formed (expt 10, Table I). The loweer ratio of α isomers to normal isomer obtained with pelargonyl chloride compared to palmitoyl chloride is attributed to the larger number of isomers possible for the latter acid chloride. It is also apparent from the data in Table I that the α-branched acid chlorides undergo decarbonylation on prolonged heating.

Evidence that the isomerization process is a reversible process was obtained by heating α-methyloctanoyl chloride under the same reaction conditions used for the isomerization of pelargonyl chloride. The ratio of branched-chain isomers to straight-chain product was of the same order of magnitude when starting with either acyl halide; compare expt 10 and 11, Table I. The branched acid chloride, however, gave rise to more octene formation.

Introduction of a phosphine ligand into the palladium salts, e.g., bis(triphenylphosphine)palladium chloride $[(C_6H_5)_3P]_2PdCl_2$, completely suppressed the isomerization and decarbonylation reactions of palmitoyl chloride at both 130 and

Table I. Isomerization of Acid Chlorides with Pd Salts[a]

Expt	Acyl halide	Registry no.	PdX_2	Registry no.	Temp, °C	Time, h	% C_nH_{2n}	% RCl	% n-RCOCl[c,d]	% α-RCOCl[c,d]
1	$CH_3(CH_2)_{14}COCl$	112-67-4	acac[b]	14024-61-4	220	1	100			
2	$CH_3(CH_2)_{14}COCl$	112-67-4	acac[b]	14024-61-4	220[e]	2	20	6	47	27
3	$CH_3(CH_2)_{14}COCl$	112-67-4	acac[b]	14024-61-4	220[e]	5	52	18	15	15
4	$CH_3(CH_2)_{14}COCl$	112-67-4	acac[b]	14024-61-4	150[e]	5	13		44	43
5	$CH_3(CH_2)_{14}COCl$	112-67-4	acac[b]	14024-61-4	150	5	14		39	47
6	$CH_3(CH_2)_{14}COCl$	112-67-4	Cl	7647-10-1	150	5	63		9	28
7	$CH_3(CH_2)_{14}COCl$	112-67-4	Br	13444-94-5	150	5	32		13	55
8	$CH_3(CH_2)_{14}COCl$	112-67-4	Br	13444-94-5	130	5	28		12	60
9	$CH_3(CH_2)_7COCl$	764-85-2	Br	13444-94-5	130	5	2		55	43
10	$CH_3(CH_2)_7COCl$	764-85-2	Br	13444-94-5	130	18	10		32	58
11	$CH_3(CH_2)_5C(CH_3)HCOCl$	43152-88-1	Br	13444-94-5	130	18	21		25	54
12	$CH_2{=}CH(CH_2)_8COCl$	27236-80-2	Br	13444-94-5	110[f]	18	8[g]		92	
13	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COCl$	112-77-6	Br	13444-94-5	150	5	15[g]		81	4

[a] Mole ratio of acid chloride to palladium catalyst of 100:1. [b] acac = acetylacetonate. [c] n-R normal isomer; α-R = α-branched isomers. [d] Determined as methyl ester. [e] Reaction run in sealed reactor. [f] At 150 °C for 18 h formed > 90% alkene. [g] Diene formation C_nH_{2n-2}.

Table II. Product Distribution of Isomerized Acyl Chlorides[a,b]

Starting n-RCOCl	% α-CH_3	% α-C_2H_5	% α-C_3H_7	% normal
$CH_3(CH_2)_7COCl$	29	17	15	39
$CH_3(CH_2)_5CHCOCl$ (with CH_3)	35	23	20	22
$CH_3(CH_2)_{14}COCl$	14	8	33[c]	45

[a] Determined by GLC of methyl esters. [b] Mole ratio of acid chloride to $PdBr_2$, 100:1 reaction run for 5 h at 130 °C. [c] Composition includes α-C_4H_9, α-C_5H_{11}, and α-C_6H_{13} isomers.

150 °C, whereas at higher temperatures decarbonylation to alkene occurred. This deleterious effect of phosphines on the isomerization of acid chlorides was further demonstrated by admixture of triphenylphosphine to the palladium bromide catalyst. This completely inhibited the isomerization of palmitoyl chloride at 150 °C, yielding only the starting acyl chloride. Substitution of a rhodium metal catalyst ($RhCl_3$) for the palladium catalyst did not produce any isomerization reaction, and the starting acyl chloride was recovered. This result is to be contrasted with the extensive use of the former transition metal as a decarbonylation catalyst at elevated temperatures.[6]

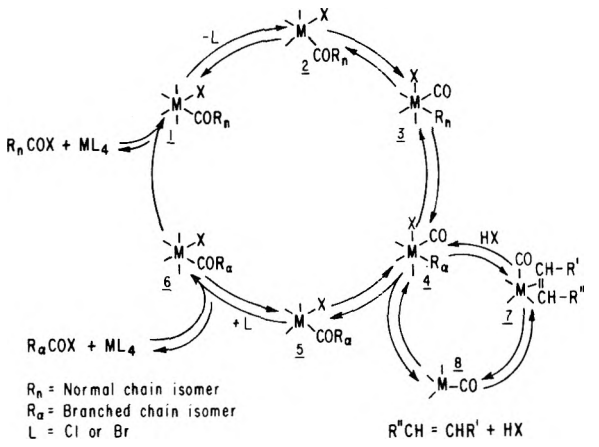
As observed with triphenylphosphine, the presence of an olefinic linkage in the acid chloride molecule also suppressed the isomerization reaction. For example, with the terminal alkene 11-undecenoyl chloride, no α isomers are observed and for the internally unsaturated acid chloride oleoyl chloride, only 4% α isomers are produced (expt 12 and 13, Table I). Attempts to increase the yields of α-branched acid chlorides for the latter two examples by raising reaction temperature or increasing reaction times resulted only in the increased formation of dienes.[7] That the double bond must be contained within the acid chloride molecule in order to effectively inhibit the isomerization reaction was demonstrated by heating pelargonyl chloride with $PdBr_2$ in the presence of either added octene-1 or octadiene. The results were similar to those obtained when no added unsaturates were present.

Insight as to the isomeric composition of the acid chlorides produced during the course of the isomerization process was obtained by the combined use of GLC and mass spectrometry. For the C_9 acid chlorides, GLC of the esterified reaction products indicated the presence of three α-branched methyl esters in addition to methyl pelargonate. The percentage distribution of this mixture of isomeric C_9 methyl esters is given in Table II. Identification of individual isomers was made from an examination of their mass spectra, more specifically by comparison of their McLafferty rearrangement ions.[8] For example, in the spectrum of methyl α-methyloctanoate this rearrangement ion is found at *m/e* 88 (base peak), thus confirming that the methyl substituent is α to the carbomethoxy function. Similarly, the α-ethyl heptanoate and α-propyl hexanoate isomers were identified by the appearance of McLafferty rearrangement ions at *m/e* of 102, 144 and 116, 130, respectively. Analysis of the palmitoyl chloride isomerization product was conducted in the same manner (Table II). A major difference in this example, however, was the formation of a larger number of α-branched isdmers. Although GLC indicated that only three isomers were formed, mass spectrometry established that the α-propyl, α-butyl, α-pentyl, and α-hexyl isomers had eluted together. Thus it appears that during the isomerization reaction all possible dialkylacetic acid isomers are formed; however, the data in Table II do suggest that branching at the 2 and 3 positions of the chain is preferred. Comparing the isomer distribution obtained for pelargonyl chloride with that of α-methyloctanoyl chloride

does not seem to indicate that the isomerization reaction is an equilibrium controlled distribution, since the isomer ratios obtained for the two starting acid chlorides are different but reproducible. During the course of the isomerization reaction, any one of the isomeric acid chlorides may undergo decarbonylation to alkene and, therefore, prevent the establishment of a true equilibrium. The major difference observed is that when starting with the branched acid chloride a larger amount of the α-ethyl and α-propyl isomers are formed.

A mechanistic rationale which readily accounts for the observed skeletal isomerization of saturated acid chlorides is shown in Scheme I. In formulating this reaction pathway the

Scheme I

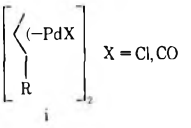


following two assumptions were made: (a) the mechanism of decarbonylation is the reverse of carbonylation,[3] and (b) the organometallic reactions shown proceed by the 16 and 18 electron rule as proposed by Tolman.[9] The initial step of this mechanism requires the oxidative addition of the acyl chloride to the four-coordinate palladium bromide catalyst to give the six-coordinate acyl–palladium complex **1**. The latter intermediate then undergoes loss of ligand to the five-coordinate species **2** which then rearranges to the six-coordinate alkyl–palladium complex **3**. The σ-bonded carbon–metal complex **3** can then readily undergo rearrangement via a hydride transfer mechanism[10] to the internally σ-bonded carbon–metal complex **4**. This step could also provide a pathway for alkene formation. The next step in this cycle is the reverse of decarbonylation, namely carbonylation to the five-coordinate complex **5** which can add a ligand to give the six-coordinate acyl–palladium complex **6** which is analogous to complex **1**. Reductive elimination of the α-branched acyl halide from complex **6** then regenerates the palladium catalyst for recycle. Since both normal and α-branched chain acid chlorides can be isomerized, all of the steps in this catalytic cycle must be reversible.

Included in Scheme I is a mechanism which accounts for the formation of alkene from either σ-bonded carbon–metal complexes **3** or **4**. As shown with complex **4**, reductive elimination of the elements of hydrogen halide leads to formation of the π-bonded alkene–palladium complex **7** which on dissociation produces the alkene and the four-coordinate palladium complex **8** which can reenter into the catalytic cycle. This latter cycle is the reverse mechanism of the carbonylation of alkenes. Accordingly, it may serve as an alternative pathway for the isomerization of acid chlorides.

The inhibition of acid chloride isomerization by phosphines can be attributed to the greater stability of transition metal complexes which contain a phosphine ligand. Whereas phosphine–metal complexes readily undergo oxidative addition with acyl chlorides to acyl metal complexes analogous to **3** (Scheme I), the latter complexes are apparently stabilized by the phosphine ligand and cannot rearrange to the branched acyl chloride. While no such acyl–palladium complexes have been isolated, the analogous acylrhodium complexes have.[11]

The reluctance of unsaturated acid chlorides to undergo acyl migration in the presence of palladium salts cannot be ascribed solely to the presence of the π bond contained within the molecule, since as noted previously, the addition of alkenes or dienes did not inhibit the isomerization of saturated acid chlorides. Since unsaturated acid chlorides can be decarbonylated to dienes,[7] oxidative addition of the unsaturated acid chloride to the metal complex must occur to give an intermediate σ complex analogous to **3** (Scheme I). The latter σ-bonded intermediate probably then rearranges rapidly via a hydride transfer mechanism to a more stable π-allylic intermediate comparable to i. It has been reported that π-allyl palladium complexes such as i undergo preferential carbonylation at C_1.[12] Such a pathway in the present study would lead to the re-formation of the normal chain acid chloride. Alternatively, it has been shown that π-allylic complexes analogous to i generally coordinate carbon monoxide weakly[13] and therefore would favor decarbonylation rather than acyl migration of the unsaturated acid chloride as is observed.



Experimental Section

Material and Equipment. Palmitoyl chloride (bp 138 °C, 0.5 mm), pelargonyl chloride (bp 58 °C, 0.4 mm), α-methyloctanoyl chloride (bp 53 °C, 0.2 mm), 11-undecenoyl chloride (bp 80 °C, 0.4 mm), and oleoyl chloride (bp 153 °C, 0.45 mm) were prepared by reaction of the free carboxylic acids with oxaloyl chloride employing the procedure of Bosshard et al.[14] $PdCl_2$ and $PdBr_2$ were obtained form Engelhard Industries, Inc., Carteret, N.J.,[15] and were used as received. Palladium acetylacetonae [$Pd(AcAc)_2$] was prepared by literature procedure.[16] Infrared spectra (ir) were obtained on a Perkin-Elmer Model 237 spectrometer using sodium chloride disks. Mass spectra were obtained on a Du Pont 21-492 double focusing instrument operating at an ionization potential of 70 eV. The gas chromatograph was a Hewlett-Packard Model 7620A instrument equipped with dual flame and thermal conductivity detectors. Separations were obtained on stainless steel columns (0.125 in. × 10 ft) containing 10% DEGS on Gas-Chrom S. Integration of peak areas was carried out with an Infotronics Model CRS-11HSB digital integrator.

Isomerization Procedures. A. Open System. Into a 25-ml round-bottom flask equipped with a magnetic stirring bar, condenser, and N_2 gas inlet tube was placed the pelargonyl chloride (3.0 g, 17 mmol) and catalyst $PdBr_2$ (45.7 mg, 0.17 mmol). The stirred mixture was then heated in a constant temperature bath at a given temperature for a specified time period (Table I). The reaction mixture was cooled to ambient temperature, and methanol (10 ml) was added. The mixture was heated to reflux for 0.5 h to ensure complete esterification. The ester mixture was transferred to a separatory funnel, diluted with water, and extracted with hexane. The combined hexane extracts were washed with H_2O until neutral, dried over $MgSO_4$, and the hexane solvent removed in vacuo to give the crude methyl ester (2.92 g). The ester mixture was then analyzed for product distribution and isomer distribution by GLC and mass spectrometry (Tables I and II).

B. Sealed System. Into a 125-ml Hasteloy-C autoclave was placed the acid chloride and metal catalyst (mole ratio of 100:1). The reactor was purged with N_2 gas, sealed, and heated by means of an electric furnace to the specified internal temperature as determined by means of a thermocouple inserted into the ouside wall of the reactor. After the specified reaction time period, the autoclave was cooled to ambient temperature, vented, and the liquid contents transferred to a flask. The crude reaction mixture was esterified and analyzed in the same manner as the product from the open flask procedure.

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Monoterpene Syntheses via a Palladium Catalyzed Isoprene Dimerization

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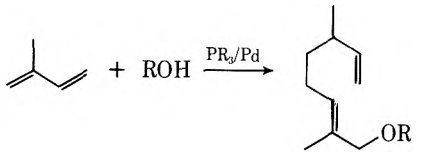
Isoprene has been reductively dimerized with formic acid and triethylamine at room temperature using 1% palladium–organophosphine catalysts, to head-to-tail dimers in up to 79% yields. The two head-to-tail dimers obtained are easily separated in high yield from the other dimers present by conversion into 7-chloro-3,7-dimethyl-1-octene with aqueous hydrochloric acid at room temperature. This chloro derivative is a convenient and practical starting material for the preparation of various terpene products. Hydroboration and pyrolysis, for example, produced a 1:3 mixture of α- and β-citronellol. *tert*-Butyl peracetate, hydrolysis, and pyrolysis gave linalool. 2,3-Dimethyl-1,3-butadiene and *cis*- and *trans*-1,3-pentadiene were also dimerized by these catalysts. Possible reaction mechanisms for the dimerization are discussed.

Several reports of transition metal catalyzed dimerizations of isoprene have appeared but yields of the dimer with the desired "head to tail" structure have generally been low and/or conversion of the dimer into useful terpene derivatives required several steps. For example, Uchida et al.[1] have reported a tetraallylzirconium–ethylaluminum sesquichloride catalyzed dimerization to 2,6-dimethyl-1,3,6-octatriene in 50% yield. The conversion of this isomer into useful terpenes probably would require several steps. Similarly, Takahashi et al.[2] have reported a dimerization catalyzed by dibromobis(diphenylphosphinoethane)palladium(II) and sodium phenoxide which produced the more desirable isomer, 2,6-dimethyl-1,3,7-octatriene, but only in 49% yield. Perhaps the most successful dimerizations were achieved in alcohol solution with triorganophosphine–palladium catalysts where ca.



75% yields of 8-alkoxy-3,7-dimethyl-1,6-octadienes were obtained.[3,4] More recently, the 8-ethoxy-3,7-dimethyl-1,6-octadiene has been converted into citronellol in three steps in 43% yield.[5] Promising dimerizations employing main group organometallics have also been reported recently.[6,7]

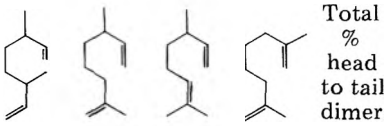
The isomeric dimers produced by palladium catalysis are clearly very dependent upon the ligands, solvent, and reaction conditions employed. Note, for example, that Josey[8] reports that in acetone solution with maleic anhydride–bis(triphenylphosphine)palladium(0) as catalyst at 105 °C isoprene gave mainly 2,7-dimethyl-1,3,7-octatriene as a product. The problem of the head to tail dimerization of isoprene with palladium catalysts seemed attractive to us because it appeared that with the proper choice of reaction conditions and ligands a practical monoterpene synthesis might be achievable.

Several of the reported palladium catalyzed dimerizations were investigated initially and eventually it was decided to concentrate on the triorganophosphine palladium salt dimerization carried out in the presence of formic acid and triethylamine which had previously been tried only with butadiene.[9,10] This reaction produced dimer dienes and carbon dioxide rather than trienes or formate esters. Preliminary experiments with isoprene indicated that good yields of head to tail dimers could be obtained under some conditions. After considerable effort, catalysts were developed which produce desirable dimers in better than 75% yields based upon the isoprene used. Experiments have determined that these dimers may be easily separated and converted into known, natural monoterpenes.

Results and Discussion

Several variables occur in the reductive diene dimerization reaction. These were investigated empirically and the results were combined in various ways to produce the most favorable yields of the desired head to tail isoprene dimers. Representative experiments of the large number carried out are shown in Table I. Very small amounts of dimers (and reduced dimers) other than those listed in Table I were observed in some experiments but these were not identified with certainty. Spectral data for the isoprene dimers and other products prepared in this investigation are listed in Table II, which will appear only in the microfilm edition of this journal. (See paragraph at end of paper regarding supplementary material.) The investigation began with the use of dichlorobis(triarylphosphine)palladium(II) complexes as catalysts. The first five entries in Table I show clear trends with changes in the para substituents in the arylphosphine ligands. The total yields of dimers decrease as the electron-donating capacity of the para substituent increases. The p-CF_3 complex gives 91% while the p-OCH_3 derivative produced only 27% dimer; the remainder of the isoprene is converted to isomeric methylbutenes. The percentage of head to tail dimers in the mixture does not vary much with these changes but, of course, the total yields based upon isoprene consumed decrease significantly, from 41 to 12% in the series. The reaction rates, on the other hand, in-

Table I. Isoprene Reductive Dimerizations

Expt no.	Catalyst	Registry no.	Solvent (22 mmol added)	Reaction time, h	% dimers	Composition of dimer mixture 	Total % head to tail dimer
1	$Cl_2[P(p\text{-}C_6H_4CF)_3]_2Pd$[a]	59840-39-0		24	91	25 38 7 25	41
2	$Cl_2[P(p\text{-}C_6H_4F)_3]_2Pd$[a]	31173-69-0		10	59	45 35 6 11	24
3	$Cl_2[P(p\text{-}C_6H_4Cl)_3]_2Pd$[a]	57457-62-2		10	73	37 35 7 17	31
4	$Cl_2[P(C_6H_5)_3]_2Pd$[a]	13965-03-2		24	24[b]	39 38 7 11	11
5	$Cl_2[P(p\text{-}C_6H_4OCH_3)_3]_2Pd$[a]	56781-20-5		24	27	57 43	12
6	$Cl_2[P(OCH_2)_3CCH_2CH_3]_2Pd$[a]	59840-37-8		24	55	28 26 22 5	31
7	$Cl_2[P(OCH_3)_3]_2Pd$[a]	30153-54-9		24	33	44 25 14 3	13
8	$Cl_2[P(O\text{-}o\text{-}C_6H_4CH_3)_3]_2Pd$[a]	41871-92-5		24	28[b]	19 34 10 21	12
9	$Cl_2[P(o\text{-}C_6H_4OCH_3)(C_6H_5)_2]Pd$[a]	59840-40-3		24	16	51 42 4 4	7
10	$Cl_2[P(o\text{-}C_6H_4CH_3)_3]_2Pd$[a]	40691-33-6		24	23[b]	40 29 17 9	11
11	$Cl_2[P(C_6H_{11})_3]_2Pd$[a]	29934-17-6		24	60	57 38 1 4	23
12	$(AcO)_2[P(C_6H_{11})_3]_2Pd$[a]	59840-38-9		7	96	38 37 3 6	38
13	$(AcO)_2[P(C_6H_5)_3]_2Pd$[a]	14588-08-0		4	56	49 33 6 8	22
14	$Cl_2[P(OCH_2)_3CCH_2CH_3]_2Pd$[a]		THF	24	89	12 40 18 13	52
15	$Cl_2[P(p\text{-}C_6H_4Cl)_3]_2Pd$[a]		THF	24	83	15 58 8 16	55
16	$(AcO)_2[P(C_6H_5)_3]_2Pd$[a]		THF	1	77	33 41 13 13	42
17	$(AcO)_2[P(C_6H_5)_3]_2Pd$[d]		THF	3	98	8 61 5 18	65
18	$(AcO)_2[P(C_6H_5)_3]_2Pd + 2\ P(C_6H_5)_3$		THF	24	10	25 62 4 9	7
19	$[P(C_6H_5)_3]_4Pd$	14221-01-3	THF	24	5	22 68 3 8	4
20	$\frac{1}{2}(\eta^3\text{-}C_3H_5PdOAc)_2 + P(C_6H_5)_3$[c,e]	12084-71-8	THF	12	93	18 64 5 14	64
21	$\frac{1}{2}(\eta^3\text{-}C_3H_5PdOAc)_2 + P(p\text{-}C_6H_4CH_3)_3$[c,e]		THF	12	97	22 61 6 11	64
22	$\frac{1}{2}(\eta^3\text{-}C_3H_5PdOAc)_2 + P(C_6F_5)_3$[c,e]		THF	12	0		0
23	$\frac{1}{2}(\eta^3\text{-}C_3H_5PdOAc)_2 + P(OCH_2)_3CCH_2CH_3$[c,d,e]		THF	12	88	3 41 21 16	54
24	$\frac{1}{2}(\eta^3\text{-}C_3H_5PdOAc)_2 + P(p\text{-}C_6H_4CF_3)_3$[c,d]		THF	2	80	35 53 13	53
25	$\frac{1}{2}(\eta^3\text{-}C_3H_5PdOAc)_2 + P(o\text{-}C_6H_4CF_3)_3$[c,d]		THF	2	68	50 22 10 11	22
26	$\frac{1}{2}(\eta^3\text{-}C_3H_5PdOAc)_2 + P(1\text{-}C_{10}H_7)_3$[c,e]		THF	12	93	30 65 5	60
27	$\frac{1}{2}(\eta^3\text{-}C_3H_5PdOAc)_2 + P(o\text{-}C_6H_5C_6H_4)_3$[c,e]		THF	12	8	68 32	3
28	$\frac{1}{2}(\eta^3\text{-}C_3H_5PdOAc)_2 + P[2,3,4,5\text{-}C_6H(CH_3)_4]_3$[c,e]		THF	16	95	13 31 20 5	47
29	$\frac{1}{2}(\eta^3\text{-}C_3H_5PdOAc)_2 + P(o\text{-}C_6H_4CH_3)_3$[c,d,e]		THF	5	98	6 55 26 12	79
30	$\frac{1}{2}(\eta^3\text{-}C_3H_5PdOAc)_2 + P(o\text{-}C_6H_4C_2H_5)$[c,e]		THF	12	95	4 42 34 6	72
31	$\frac{1}{2}(\eta^3\text{-}C_3H_5PdOAc)_2 + P\{2,5\text{-}C_6H_3[CH(CH_3)_2]_2\}_3$[c,e]		THF	12	71	11 45 36 1	58
32	$\frac{1}{2}(\eta^3\text{-}C_3H_5PdOAc)_2 + P\{2,5\text{-}C_6H_3[CH(CH_3)_2]_2\}_3$[c,d,e]		THF	12	98	18 37 33 1	68
33	$\frac{1}{2}(\eta^3\text{-}C_3H_5PdOAc)_2 + \frac{1}{2}P(o\text{-}C_6H_4CH_3)_3$[c,d,e]		THF	12	59	21 40 10	36
34	$\frac{1}{2}(\eta^3\text{-}C_3H_5PdOAc)_2 + P(CH_2CH_2CN)_3$[c,d,e]		THF	1.5	90	48 44 4 5	43
35	$Pd(OAc)_2 + P(o\text{-}C_6H_4CH_3)_3$[e,f]	127-08-2	THF	5	85	18 42 31 7	62
36	$\frac{1}{2}(\eta^3\text{-}C_3H_5PdOAc)_2 + P(2\text{-}CH_3, 5\text{-}CF_3C_6H_3)_3$[c,d,e]		THF	12	84	1 33 32 23	55

[a] Reaction carried out in a 30-ml capped, heavy-walled Pyrex tube with 0.069 mmol of catalyst, 11 mmol of triethylamine, 10 mmol of isoprene, and 0.5 ml of 98% formic acid under an argon atmosphere at 40–45 °C except where noted. [b] Yield of isolated dimer mixture. [c] Reaction carried out in a 30-ml capped, heavy-walled Pyrex tube with 0.065 mmol of $(\pi\text{-}C_3H_5PdOAc)_2$ and 0.128 mmol of triorganophosphine, 11 mmol of triethylamine, 10 ml of isoprene, and 0.5 ml of 98% formic acid under an argon atmosphere at 40–45 °C unless otherwise noted. [d] Formic acid added last in 50-μl amounts every 15 min. [e] Carried out at 20–25 °C. [f] The amount of catalyst employed was 0.128 mmol. The reaction was otherwise the same as *a*.

crease with increasing electron-donating ability of the substituents.

Steric effects upon the isoprene dimerization were investigated in experiments 6–11. These effects are apparently not separable from electronic effects and no clear trends can be observed. Similar total yields of dimers are obtained from the smallest ligand investigated, $P(OCH_2)_3CCH_2CH_3$, and the largest one looked at, $P(C_6H_{11})_3$. Much more head to head dimer is produced with the larger ligand, however.

The anion present in the catalyst proved to be an important variable. Both reaction rates and product composition are significantly affected. changing the anions from chloride to acetate increases reaction rates by a factor of about 10 in the two cases studied as can be seen by comparing the results of

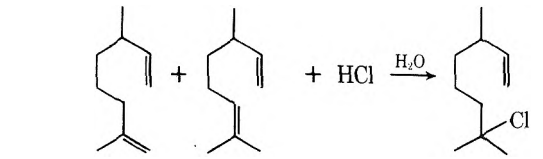
experiments 4 and 13, and 11 and 12. In both cases, the change to the acetate complex also significantly increases the yields of head to tail dimers obtained.

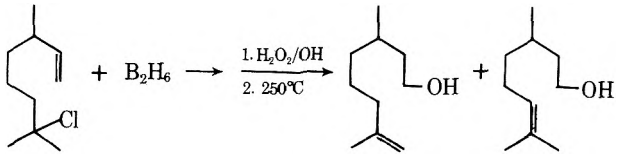
The use of THF as a solvent also has been shown to be beneficial, particularly when acetate complexes are used as catalysts. Total yields of dimers and relative yields of head to tail dimers improve upon addition of THF. The effect of THF can be seen by comparing experiments 14 with 6, 15 with 3, and 16 with 13. At this point the remarkable improvement produced by adding the formic acid slowly rather than all initially was discovered. Experiment 16 with diacetatobis(triphenylphosphine)palladium(II) as catalyst, with an initial 2.6 equiv of formic acid added, gave a 77% yield of dimers with a total yield of head to tail dimers of 42%. Slow addition of the same amount of formic acid, experiment 17, improves the total yield to 98% and the head to tail dimer yield to 65%. This effect was subsequently found to be more the result of the amount of acid added initially rather than the rate of addition. The use of 1 equiv of formic acid initially substantially improves the yield of diene dimer over the reaction with 2.6 equiv. The slow addition of the 1 equiv of acid improves the yields somewhat more but this procedure significantly increases the tme required to complete the reaction. The major influence of reducing the formic acid concentration is to decrease the amount of methylbutenes formed.

The triorganophosphine to palladium ratio was found to be another, very important, variable. Addition of 2 equiv of triphenylphosphine to reaction 16, in which 77% dimers were obtained, lowers the yield of dimers to only 10% (experiment 18). There is a corresponding increase in the yield of methylbutenes obtained. Similarly, the use of tetrakis(triphenylphosphine)palladium(0) as catalyst produces only 5% dimers and 95% methylbutenes (experiment 19). Lowering the phosphine to palladium ratio below 2:1 improves yields further. A ratio of 1:1 proved to be optimum. For these experiments, "π-allylpalladium acetate dimer"[11] has been employed with the organophosphine being added separately to the reaction mixtures. Experiments 20–34 illustrate the improvements brought about with lower PR_3:Pd ratios sometimes combined with slow addition of the formic acid. Changes in the para substituent of the phosphine now show smaller effects than in the 2:1 catalysts, but distinct trends are not seen. Steric effects appear to be more significant with the 1:1 than with the 2:1 catalysts, with the tri-o-tolylphosphine ligand being about the best (experiment 29). With slow addition of the formic acid this catalyst produces head to tail dimers in 79% yield based upon the isoprene added.

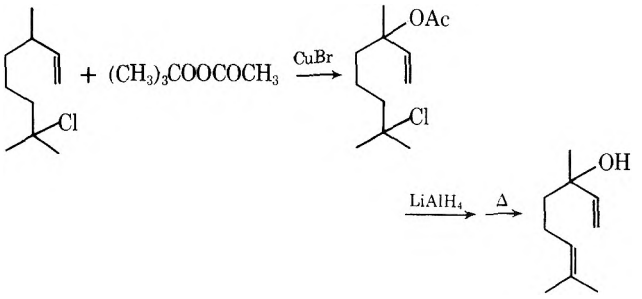
The selectivity of the dimerization to head to tail products is also improved slightly by lowering reaction temperatures from 40–45 °C to 20–25 °C.

The dimerization shown in experiment 29 has been scaled up and carried out with 0.50 mol of isoprene. There was obtained an 87% isolated yield of dimer which contained 71% head to tail isomers. While the isomeric dienes could be separated by careful fractional distillation, for the purpose of preparing terpene derivatives this was not necessary. The mixture was found to be converted into easily separable products if it was reacted with concentrated aqueous hydrochloric acid at room temperature. Only the di- and trisubstituted double bonds reacted to form tertiary chlorides while the terminal, monosubstituted double bonds were unaffected. Thus, the head to head dimer remained unchanged after HCl treatment, the tail to tail isomer formed a dichloride, and the desired head to tail dimers both gave the same monochloride. These reaction products were very easily separated by distillation under reduced pressure. The monochloro product, 7-chloro-3,7-dimethyl-1-octene, was isolated in 84% yield based upon the head to tail dimers present. This monochloride is a convenient starting material for terpene syntheses. Reaction with diborane, for example, followed by oxidation and pyrolytic dehydrohalogenation at 250 °C produced an approximately 1:3 mixture of α- and β-citronellols in 70% yield.

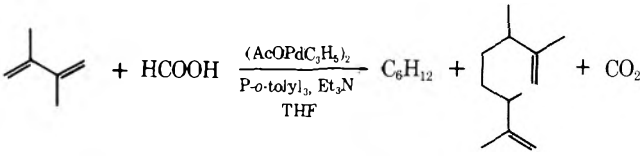




About 5–10% of secondary alcohol also appeared to be formed in the hydroboration, as expected. The monochloro compound was also oxidized with *tert*-butyl peracetate and a cuprous bromide catalyst to the chloro acetate which was reduced with $LiAlH_4$ and pyrolyzed to linalool in 64% overall yield.

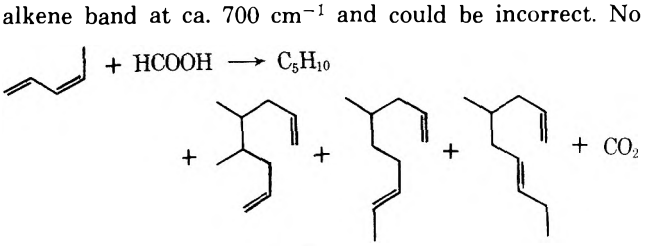


The utility of the reductive dimerization reaction for dimerization of dienes other than butadiene and isoprene has also been explored briefly. Both 2,3-dimethyl-1,3-butadiene and *cis*- and *trans*-1,3-pentadiene were found to dimerize slowly with the π-allylpalladium acetate dimer–tri-*o*-tolylphosphine catalyst in yields of 42, 67, and 68%, respectively. The dimethylbutadiene, as might have been expected, gave



largely 2,3,6,7-tetramethyl-1,7-octadiene while the pentadienes gave mixtures of at least three compounds.

The major product from *cis*-1,3-pentadiene (65% of dimers) proved to be 4,5-dimethyl-1,7-octadiene. The other dimers appeared to be *trans*-4-methyl-1,7-nonadiene (24%) and *trans*-4-methyl-1,6-nonadiene (8%). The assignment of stereochemistry is based only upon the absence of the cis-alkene band at ca. 700 cm^{-1} and could be incorrect. No



isomerization of unreacted *cis*-pentadiene was observed at 25 °C during the dimerization.

Under the same conditions *trans*-1,3-pentadiene gave the same three major dimers but in different amounts. The major isomer was *trans*-4-methyl-1,7-nonadiene (72%). The 1,6-diene was formed in 20% yield while the 4,5-dimethyl isomer was obtained in only 8% yield. No isomerization of the *trans*-pentadiene was observed at 25 °C. At 40 °C, however,

Table III. 1,3-Pentadiene Reductive Dimerizations[a]

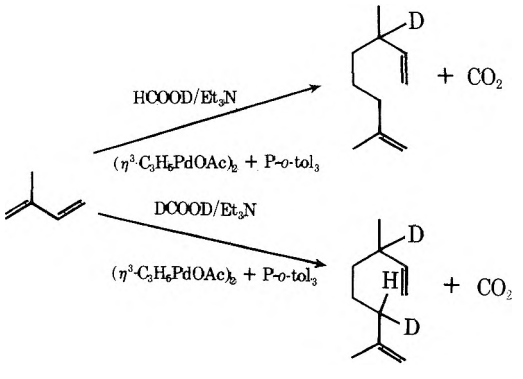
Isomer	Catalyst	Temp, °C	Reaction time, h	% dimers	Composition of dimer mixture		
Cis	½(η^3-$C_3H_5PdOAc)_2$ + $P(p\text{-}FC_6H_4)_3$	25	70	52	38	41	19
Trans	½(η^3-$C_3H_5PdOAc)_2$ + $P(p\text{-}FC_6H_4)_3$	25	70	59	6	67	27
Cis	½(η^3-$C_3H_5PdOAc)_2$ + $P(o\text{-}CF_3C_6H_4)_3$	25	70	4	100		
Trans	½(η^3-$C_3H_5PdOAc)_2$ + $P(o\text{-}CF_3C_6H_4)_3$	25	70	0			
Cis	½(η^3-$C_3H_5PdOAc)_2$ + $P(o\text{-}CH_3C_6H_4)_3$	25	69	67	65	24	8
Trans	½(η^3-$C_3H_5PdOAc)_2$ + $P(o\text{-}CH_3C_6H_4)_3$	25	69	68	8	72	20
Cis	½(η^3-$C_3H_5PdOAc)_2$ + $P(o\text{-}CH_3C_6H_4)_3$	40[b]	20	42	49	34	15
Trans	½(η^3-$C_3H_5PdOAc)_2$ + $P(o\text{-}CH_3C_6H_4)_3$	40	20	49	2	71	27

[a] Reaction conditions: 0.069 mmol of catalyst, 11 mmol of triethylamine, 10 mmol of diene, and 0.5 ml of 98% formic acid carried out under argon. [b] *cis*-1,3-Pentadiene isomerized to the trans isomer during the reaction as determined by VPC.

cis-1,3-pentadiene was isomerized to the trans isomer during the dimerization. Even at 40 °C, however, there was still a substantial difference in the composition of the product mixtures obtained from the two isomeric pentadienes. The results obtained in the above experiments and with a few other catalysts are listed in Table III.

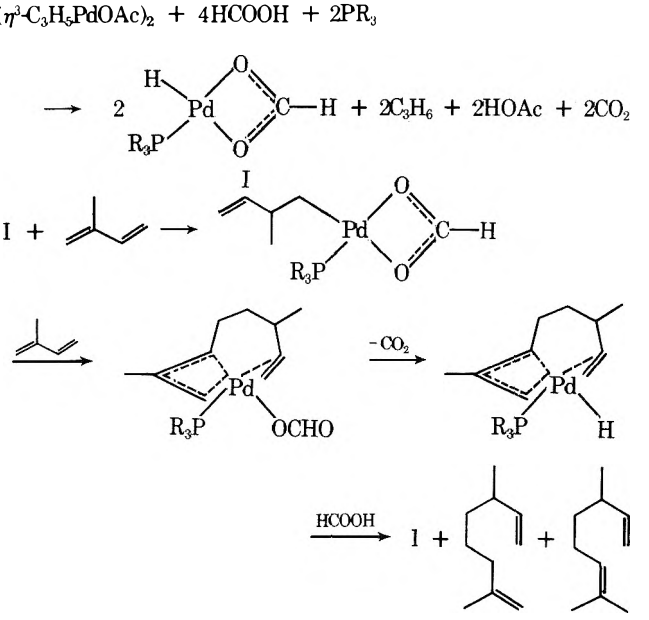
Dimerization did not occur under the above conditions with 1,3-cyclohexadiene, *trans,trans*-2,4-hexadiene, or myrcene. In all cases, CO_2 was evolved suggesting that reduction took place.

Mechanism of Reductive Dimerization. Various attempts to isolate pure organometallic intermediates from the dimerization of isoprene were unsuccessful. Only amorphous, unstable materials could be obtained. Some useful information was gained by carrying out the dimerization in the presence of deuterated formic acid, however, Reactions similar to experiment 29 were carried out with both dideuterated and carboxyl deuterated formic acid. The carboxyl deuterium was



found on carbon 6 and the other deuterium on carbon 3 of the 2,6-dimethyl-1,7-octadiene chain.

Two mechanisms appear reasonable to consider for this dimerization. In both, palladium(0) is a necessary starting material. Palladium metal was shown to be formed within 5 min when formic acid was added to the usual reaction mixtures at 25 °C without the diene being present. In one mechanism formic acid may add oxidatively to the Pd(0) phosphine complex to form a hydridoformatopalladium(II) complex which reacts with isoprene to produce a formato(methylbutenyl)palladium complex. This complex could then add to a second isoprene, perhaps forming a chelated complex, which ultimately decomposes by losing CO_2 and reductively eliminating the diene dimer. The deuterium experiments are consistent only with metal hydride addition to the disubstituted isoprene double bond initially. A possible formulation is the following.



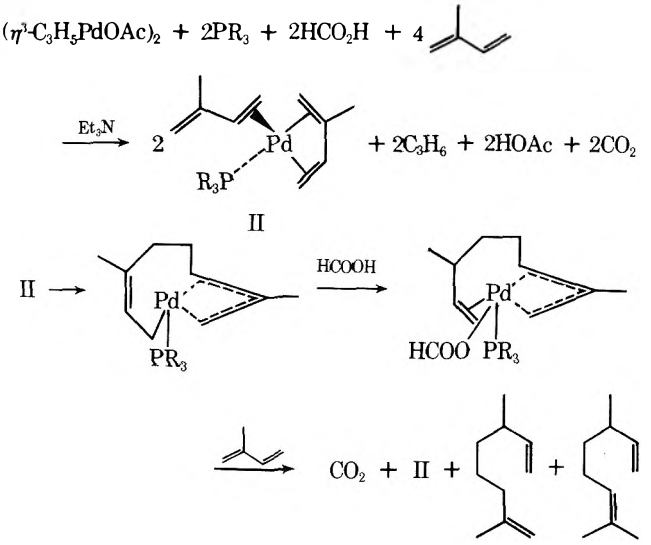
The function of the tertiary amine would be to allow the formation of a small equilibrium concentration of formic acid necessary to produce I but not have enough present to react rapidly with the methylbutenylpalladium intermediate and form methylbutenes. The preference for addition of the metal hydride to the disubstituted double bond of isoprene is difficult to explain. Results from presumed hydridohalopalladium catalyzed carbonylations of dienes do not appear consistent with the above proposed mechanism. Carbonylation of butadiene in methanol at 70 °C gives entirely methyl 3-pentenoate[12] rather than the 4-pentenoate required to be consistent with the above mechanism. Isoprene under similar conditions gave three isomeric esters. The formation of the

$$CH_2{=}CHCH{=}CH_2 + CO + CH_3OH \xrightarrow[1000\ psi,\ 70°C]{[Bu_3PPdI_2]_2} CH_3CH{=}CHCH_2COOCH_3$$

major product, methyl 4-methyl-3-pentenoate,[12] is also not consistent. The carbonylation of *trans*-1,3-pentadiene in ethanol likewise produced only ethyl 2-methyl-3-pentenoate,[13] a product not expected if the pentadiene dimerization proceeds by an initial 1,2-hydridopalladium addition to the more substituted double bond. While these results do not necessarily rule out the above mechanism, the second mechanism below appears to better explain the facts.

The other mechanism we consider possible involves coupling of two isoprene units on Pd)0) to form a dimethylocta-

dienediylpalladium(II) complex which is then reduced by formic acid with CO_2 elimination. The intermediate bisallylic complex would be analogous to the isolated nickel complex obtained in the reaction of isoprene with triphenylphosphine-1,5,9-cyclododecadienenickel(0)[14] with a similar mechanism of formation as suggested by Wilke et al.[15] A possible formulation for the palladium catalyzed reaction is the following.



The tertiary amine would be necessary to reduce the formic acid concentration, so that II undergoes coupling rather than reduction by reacting with formic acid.

In either mechanism, formation of the minor, second isomeric head to tail dimer could occur by hydrogen transfer to the primary end of the π-allylic group rather than the secondary end.

The details as to why the head to tail isoprene dimers are preferentially formed with some catalysts and not with others remain to be explained. It is clear that both chloride ligands and more than one organophosphine ligand per palladium favor formation of methylbutenes rather than dimers. A competition appears to exist between dimerization and reduction. If the dimerization is prevented or inhibited by the presence of an excess of "good ligands" (such as phosphine or chloride ion) which take up coordination positions required by the second diene unit, then reduction appears to occur. The coupling of the diene units would seem to be best explained by formation of a tetrahedral intermediate such as II where an η^4 diene reacts with an η^2 diene ligand. If both dienes were only η^2 and coupling occurred through the uncoordinated double bonds, it would be difficult to explain why one diene would be attached at the monosubstituted double bond and the other at the disubstituted one, particularly when increasing the steric bulk of the phosphine group would require an increase in coordination to the disubstituted double bond. Electronic and steric effects in the phosphine would be felt by both the η^4 and η^2 dienes and their orientations with respect to each other would be influenced by these factors. Coupling will presumably occur between the ends of the diene units closest together.

The dimeric products obtained from 2,3-dimethylbutadiene and the 1,3-pentadienes are explicable in terms of the mechanism proposed above for the isoprene dimerization. The formation of some of the same three isomeric products from both *cis*- and *trans*-1,3-pentadienes simply may be the result of a partial isomerization of the cis to the trans isomer on the catalyst before dimerization occurs. Alternatively, the expected intermediates for the formation of the two methylnonadienes may be isomerized through π to σ allylic transformations with bond rotations. If equilibration were rapid compared to reduction the same ratio of the 4-methyl-1,6-nonadiene to the 1,7-diene would be expected from both the *cis*- and *trans*-1,3-pentadiene and this is approximately correct as shown in Table II.

Experimental Section

Reagents. Isoprene, formic acid (98%), and 2,3-dimethylbutadiene were obtained from the Aldrich Chemical Co. and used without further purification. The triethylamine was obtained from the Eastman Organic Chemicals Co. and dried over molecular sieves (4 Å). The THF was obtained from the Fisher Scientific Co. and used without further purification except when used in the deuteration experiments, when it was dried over the sodium benzophenone ketyl. Formic acid-d_2 was obtained from Stohler Isotope Chemicals. Formic acid-O-d_1 was obtained by treating excess sodium formate with trifluoroacetic acid-d_1 and distilling the volatile material at 25 mm. *cis*- and *trans*-1,3-pentadiene were obtained from the Chemical Samples Co. Catalysts of formula L_2PdCl_2 were obtained by treating $(PhCN)_2PdCl_2$ with 2 equiv of the phosphine in benzene and filtering the resulting precipitates. The catalysts were routinely recrystallized from CH_2Cl_2/hexane. Complexes of the form $L_2Pd(OAc)_2$ were prepared by treating $Pd(OAc)_2$ in benzene with 2 equiv of the phosphine and recovering the resulting solid by concentrating the solution. The $[(\eta^3\text{-allyl})PdOAc]_2$ dimer was prepared according to the method of Robinson and Shaw.[9] The tri-*o*-ethylphenylphosphine, tri-2,3,4,5-tetramethylphenylphosphine, tri-*o*-phenylphenylphosphine, and the tri-2,5-diisopropylphenylphosphine were prepared by the Grignard reaction of the bromides with phosphorus trichloride in THF. Other phosphines and phosphites were commercially available from the Alfa Chemical Corp.

General Procedure for Small-Scale Reductive Dimerization. Reactions were carried out in 30-ml heavy-walled Pyrex tubes which had a lip around the opening so that the tubes could be sealed with rubber-lined bottle caps. The catalysts, 0.069 mmol, and a magnetic stirring bar were placed in the tube and the system purged with argon. The tube was then quickly capped and 1.6 ml (11 mmol) of triethylamine, 1 ml (10 mmol) of isoprene, and ca. 0.13 g of 1,3,3,4-tetramethylpentane as internal standard were injected by means of syringes through a small hole in the metal cap on the tube, through the rubber liner. The formic acid could now be introduced all at once, 0.5 ml (13 mmol) usually or in 50-μl portions at 15-min intervals while the reaction mixture was stirred at the required temperature. If solvent was used it was added before the formic acid. Two liquid phases were usually noted when the formic acid was all added initially. The rate of the reactions could be conveniently measured by noting the rate of pressure increase in the tubes due to formation of carbon dioxide. In our reaction vessels 30–50 psig developed depending upon the reaction temperature. Pressure gauges attached to syringe needles were inserted in the reaction tubes to measure the pressure changes. Reaction mixtures were analyzed by VPC directly with reference to the internal standard present. Analyses were carried out on a 10-ft DC 550 column at 120 °C. The major isoprene products eluted in the following order: 3,6-dimethyl-1,7-octadiene, 3,7-dimethyl-1,7-octadiene, 3,7-dimethyl-1,6-octadiene, and 2,7-dimethyl-1,7-octadiene.

7-Chloro-3,7-dimethyl-1-octene. In a 500-ml three-necked round-bottomed flask equipped with a mechanical stirrer, dry ice condenser attached to an argon cylinder, and a gas bubbler outlet were placed 0.95 g (2.3 mmol) of acetato-η^3-allylpalladium(II) dimer,[11] 1.41 g (4.6 mmol) of tri-*o*-tolylphosphine, 90 ml of tetrahydrofuran, 80 ml of triethylamine, and finally 50 ml (0.3 mol) of 98% formic acid was added dropwise over a period of 2–3 h. After stirring for a total of 5 h VPC analyses showed that all of the isoprene had reacted. The total reaction mixture was then subjected to distillation under reduced pressure. The tetrahydrofuran and amine were removed at 25–30 °c at 40 mm. The higher boiling fraction, bp up to 60 °C at 20 mm, was the isoprene dimer mixture. There was obtained 30.1 g (87.5% based upon the isoprene used). VPC analyses showed the product to contain 72% of the two isomeric head to tail dimers.

The entire dimer product was then added to 120 ml of concentrated hydrochloric acid and the two-phase mixture was stirred at room temperature for 24 h. The reaction mixture was next diluted with 200 ml of water and extracted three times with ether and the combined extracts were washed with saturated aqueous sodium bicarbonate. After drying over anhydrous magnesium sulfate, the ether was removed on a rotary evaporator at room temperature and the residue was distilled under reduced pressure through a short Vigreux column. There was obtained 1.83 g of 3,6-dimethyl-1,7-octadiene, bp 30–35 °C (9 mm), 22.7 g (84%) of 7-chloro-3,7-dimethyl-1-octene, bp 55–60 °C (9 mm), and 11 g of 2,7-dichloro-2,7-dimethyloctane, bp 90–102

°C (9 mm). The latter compound crystallized on cooling in the freezer.

Anal. Calcd for $C_{10}H_{20}Cl_2$: C, 56.87; H, 9.47. Found: C, 57.13; H, 9.65.

Preparation of Citronellol. A solution of 5.0 g (28.6 mmol) of 7-chloro-3,7-dimethyl-1-octene and 4.65 g (123 mmol) of sodium borohydride in 150 ml of THF was stirred while 16.5 ml (105 mmol) of boron trifluoride etherate was added dropwise. After the addition, stirring was continued for 1 h. Then a solution of 4 g of sodium hydroxide in 50 ml of water was added slowly (foaming). After the addition, 33 ml of 30% hydrogen peroxide was added. Stirring was continued at room temperature for 1 h and then at reflux temperature for 3 h. Addition of water and extraction with ether gave 6.05 g of crude chloro alcohol after evaporation of the solvent. Attempts to dehydrohalogenate with alcoholic potassium hydroxide gave only low yields of the desired products. Better results were obtained by pyrolysis in a gas chromatograph. With an inlet temperature of 250 °C on a 10-ft 20% Carbowax 20M column at 200 °C, a 70% yield of a mixture of α- and β-citronellol was obtained. The β isomer predominated in about a 3:1 ratio over the α. The NMR spectra of the products confirmed their identities. About 10% of another isomeric product was also present. It was probably secondary alcohol from addition of boron to the secondary position of the chloro olefin.

Preparation of Linalool. A mixture of 1.90 g (10.9 mmol) of 7-chloro-3,7-dimethyl-1-octene and 0.111 g of cuprous bromide was stirred and heated on a steam bath while 0.586 g (4.44 mmol) of *tert*-butyl peracetate was added dropwise over a period of 10 min. Heating was continued for 3 h. After cooling to room temperature a solution of 0.10 g of sodium iodide in 3 ml of acetic acid containing a trace of ferric chloride was added to decompose the excess perester. The resulting mixture was diluted with aqueous sodium carbonate and the products were extracted with ether. After drying over anhydrous magnesium sulfate, the solvent was evaporated and the red-brown oil remaining was rediissolved in ether and added to 0.57 g (15 mmol) of lithium aluminum hydride in 10 ml of ether. After stirring at room temperature for 2 h, water was added. The ether phase was separated and the aqueous residue was extracted again with ether. The combined extracts were dried and concentrated. The chloro alcohol so obtained was readily pyrolyzed in the gas chromatograph to linalool. Analyses by gas chromatograph on a 9-ft 20% SE-30 on Chromosorb W column at 175 °C (inlet 175 °C) indicated that a 64% yield of linalool had been obtained. Isolation of a sample of the product by preparative GLC and comparison of the NMR spectrum with that of authentic linalool showed the materials to be identical. Two other minor products were also present which were not identified.

Isoprene Reductive Dimerization with Deuterated Formic Acids. Reaction with both mono- and dideuterated formic acid were carried out as in experiment 20 in Table I. Products were isolated by diluting the reaction mixture with 50 ml of water, extracting with 100 ml of ether, washing the extracts with 2 N hydrochloric acid, and drying over anhydrous magnesium sulfate. The ether was evaporated and the deuterated 2,6-dimethyl-1,7-octadiene was isolated from the product mixture by preparative VPC on a 10-ft DC-550 column at 120 °C. Comparison of the NMR spectra of the deuterated products with the undeuterated ones indicated the position of the deuteriums. The 2,6-dimethyl-1,7-octadiene product was 72% monodeuterated, 27% undeuterated, and 4% dideuterated when HCOOD was used and 87% dideuterated, 3% mono- and 10% tetradeuterated when DCOOD was used as determined by mass spectroscopy.

Reductive Dimerization of 2,3-Dimethyl-1,3-butadiene. To a 30-ml Pyrex tube containing a magnetic stirring bar, as described in the general procedure for isoprene dimerization above, was added 0.057 g (0.13 mmol) of acetato-η^3-allylpalladium dimer,[11] 0.078 g (0.26 mmol) of tri-*o*-tolylphosphine, 3.6 ml of tetrahydrofuran, 3.2 ml of triethylamine, 2.3 ml (20 mmol) of 2,3-dimethyl-1,3-butadiene, and 0.025 g (1.93 mmol) of 2,3,3,4-tetramethylpentane as internal standard. The mixture was stirred in the capped tube under argon at room temperature and 0.5 ml (0.13 mmol) of 98% formic acid was added. Three days were required for complete reaction. VPC analysis then showed a 42% yield of one dimer and <5% of another formed.

The products were isolated as in the experiments described above with deuterated formic acid. Only the major product could be isolated in sufficient quantity to be identified by NMR. (See Table II for spectrum.) The molecular weight determined by high-resolution mass spectroscopy was 166.172 (calcd, 166.172).

Reductive Dimerization of *cis*- and *trans*-1,3-Pentadiene. These reactions were carried out exactly as in the preceding experiment using 2 ml (20 mmol) of the diene in place of the dimethylbutadiene. Three days were required for complete reaction. The major products were isolated by preparative VPC. Identification was made from ir and NMR spectra (See Table II) and molecular weights.

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Supplementary Material Available. Table II, a listing of NMR, ir, and mass spectroscopy data for the products prepared in this study (3 pages). Ordering information is given on any current masthead page.

Registry No.—Respective compounds in Table II, 59840-09-4, 6874-35-7, 2436-90-0, 59840-10-7, 59840-11-8, 59840-12-9, 106-22-9, 141-25-3, 59840-13-0, 59840-14-1, 59840-15-2, 59840-16-3; isoprene, 78-79-5; *cis*-1,3-pentadiene, 1574-41-0; *trans*-1,3-pentadiene, 2004-70-8.

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Stereoselective Reduction of Menthone and Isomenthone by Dissolving Alkali Metals and by Hydrogen with Group 8 Metals on Carbon

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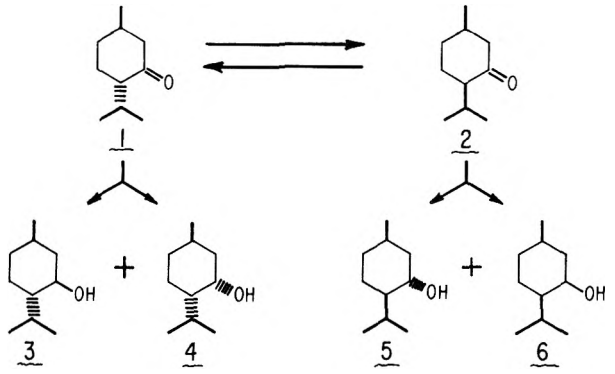
The reduction of menthone–isomenthone mixtures has been studied with hydrogen in the presence of ruthenium, rhodium, and platinum on carbon and with the dissolving alkali metals Na, K, and Li in a variety of media. The only system to afford a stereospecific reduction to menthol was lithium in liquid NH_3 at −78 °C. Several other systems showed high selectivity for the production of menthol or neomenthol from menthone and for the production of isomenthol or neoisomenthol from isomenthone.

The stereochemistry of the reduction of substituted cycloalkanones to produce a mixture of epimeric alcohols has been the subject of many investigations.[1] The specific problem of the stereospecific reduction of menthone (**1**) is a separate facet of the cycloalkanone area and has received the attention of many workers.[2]

The stereoselectivity problem in the menthone reduction case is especially challenging in that only one of the four observed products, menthol (**3**), is of commercial significance. One needs to prevent the reduction of menthone to neomenthol (**4**) and also to prevent menthone epimerization to isomenthone (**2**) with resultant reduction of **2** to isomenthol (**5**)

Scheme I



and neoisomenthol (**6**). Indeed, a great amount of effort appears to have been expended in attempts to reduce the contamination of menthol by **4**, **5**, and **6**.[2]

The accuracy of the diastereomeric alcohol distributions reported in prior work can be seriously questioned because many of the analytical methods employed were merely rough approximations. Recently, however, Gillen and Scanlon[3] have reported an excellent, reliable, and reproducible gas chromatographic method for the single analysis of all six expected components of menthone–isomenthone reduction mixtures, i.e., both ketones and all four alcohols. This development has allowed us to undertake a thorough examination of the reduction of menthone–isomenthone mixtures by the dissolving alkali metal method and also by hydrogenation over transition metal catalysts on carbon.

Since menthone and isomenthone can be fully equilibrated with each other, one can study a reduction of either a menthone–isomenthone mixture or a sample of pure menthone and still obtain useful information regarding the stereoselectivity of the menthone reduction.[4] In our studies we examined the reduction of an equilibrated menthone–isomenthone mixture (70:30 ratio) and the reduction of a very high percentage menthone mixture (98.6:1.4 ratio)[4] for the alkali metal systems. Hydrogenations with group 8 metals were performed with an equilibrated ketone mixture only.

Results and Discussion

A. Dissolving Alkali Metals. Table I lists a series of dissolving metal reductions performed with Na, K, Li in wet ether, alcohols, or liquid ammonia. The best results were obtained with lithium metal in liquid NH_3[5] at −78 °C (run 1), which gave a stereospecific reduction of menthone to menthol. Reduction at −30 °C was 98% stereoselective.

The relative stereoselectivities of the reduction of each ketone[6] are expressed in terms as follows:

$$\text{stereoselectivity of menthone reduction to menthol} = \frac{\%\ \text{menthol}}{\%\ \text{menthol} + \%\ \text{neomenthol}}$$

$$\text{stereoselectivity of isomenthone reduction to isomenthol} = \frac{\%\ \text{isomenthol}}{\%\ \text{isomenthol} + \text{neoisomenthol}}$$

Stereoselectivities expressed in this manner are listed for all the runs in Table II.

From these data it can be seen that, with two exceptions, the stereoselectivity of the reduction of menthone to menthol ranges from 87 to 100% and in Li/liquid NH_3 was 100% in all cases. The main pathway for reduced menthol yield in these systems lies in the epimerization of menthone to isomenthone. The resultant formation of the alcohols **5** and **6** via reduction of isomenthone is highly selective to isomenthol only with the Li/liquid NH_3 method; the rest of the data represent a scatter of results.

The greater degree of selectivity in the reduction of menthone can be attributed to the fact that the alcohol so favorably produced, menthol, is the only one of the diastereomers capable of an all-equatorial configuration. If the path of reduction involves initial metal atom approach to the oxygen atom of the carbonyl group, one would expect the metal–alkoxy radical anion thus formed to favor a configuration with the alkoxy function in the equatorial position, if possible. This would result in a large preference for formation of menthol rather than neomenthol.

Isomenthol and neoisomenthol can each have two groups in the equatorial position and the reduction of isomenthone would not be expected to be so stereoselective. However, one would expect a bias in the direction of isomenthol as the alkoxy function would then be paired with the larger isopropyl group rather than the smaller methyl group as in neoisomenthol. The results generally support this expectation, except for the reductions involving sodium in methanol or ethanol at 0 °C which afford almost equal amounts of **5** and **6**. The fact that these same reagents afford an excess of **5** at reflux temperature suggests the possibility that a kinetically con-

Table I. Dissolving Metal Reductions of Menthone–Isomenthone Mixtures

Run no.	Ketone mixture[d]	Metal	Solvent	Temp, °C	Redn,[a] %	Product distribution, % Menthol	Neomenthol	Isomenthol	Neoisomenthol
1	A	Li	Liq NH_3	−78	100	98.6		1.4	
2	A	Li	Liq NH_3	−30	100	96.8		3.2	
3	B	Li	Liq NH_3	−78	100	71		29	
4	A	Na	EtOH	0	73[b]	82	2.5	7.5	8
5	A	Na	MeOH	0	51[b]	54	12	17	17
6	B	Na	MeOH	0	39	65	7	13.5	14.5
7	B	Li	Wet ether	0	30[c]	65	10	15	10
8	B	Li	Wet ether	Ambient	87[c]	74	9	13	4
9	B	Li	EtOH	Reflux	No redn[b]				
10	A	K	Wet ether	Ambient	70[b]	85	2	11	2
11	B	K	Wet ether	Ambient	65[b]	76	4.5	15	4.5
12	A	K	EtOH	0	83[b]	83	3	10	4
13	B	K	EtOH	0	71	71	4	16	9
14	B	K	EtOH	Reflux	72	65	6	20	9
15	B	Na	Wet ether	0	94	79	5	12	4
16	A	Na	Wet ether	0	99	87.5	3	7.5	2
17	A	Na	Wet ether	Ambient	100	86	2	10	2
18	B	Na	$CH_3CHOHCH_3$	Reflux	99[b]	60	15	17	8
19	B	Na	EtOH	0	69	74	4	13	9
20	B	Na	EtOH	Reflux	84	70	5	20	5
21	B	Na	Wet ether	Ambient	91	75	4	15.5	5.5

[a] Unless otherwise indicated, reaction used 2 equiv metal/equiv ketone. [b] 2.5 equiv metal. [c] 3.0 equiv metal. [d] A, 98.6:1.4 mixture; B, 70:30 mixture.

Table II. Stereoselectivity in the Reduction of Menthone and Isomenthone[a]

Run no.[b]	% menthone to menthol	% isomenthone to isomenthol
1	100	100
2	100	100
3	100	100
4	97	48
5	82	50
6	92	48
7	87	60
8	89	76
9		
10	98	85
11	94	77
12	97	71
13	95	64
14	92	69
15	94	75
16	97	79
17	98	83
18	80	68
19	95	59
20	93	80
21	95	74

[a] As defined in the text. [b] Identical with run numbers in Table I.

trolled distribution of the two alcohols is obtained at 0 °C and that the alcohols are equilibrated via the ketone to a thermodynamic distribution at reflux. Unfortunately, a straightforward test of this possibility vs. other explanations does not appear likely judging by the extensive mechanistic discussions in ref 5.

We did not pursue the use of sodium, potassium, or rubidium in liquid ammonia as the use of lithium achieved our synthetic goal of stereospecific reduction of menthone to menthol.

B. Hydrogen with Group 8 Metals on Carbon. Reductions of menthone–isomenthone mixtures were conducted over rhodium, ruthenium, and platinum on charcoal in protic media (generally aqueous) usually containing added acid or base. Temperatures ranged from 105 to 190 °C and pressures from 75 to 500 psig. Conversions were high, generally over 90% in less than 24 h.

While no conditions were found which afforded a high selectivity to menthol, especially in comparison with the dissolving metal reductions, systems were found which would clearly afford highly selective syntheses of each of the diastereomeric alcohols **4**, **5**, and **6** given a supply of pure menthone or isomenthone. Data are given in Tables III–V for reductions under neutral, basic, and acidic conditions, respectively, and are further broken down into groups according to the metal employed.

The most selective catalyst system for the production of menthol (**3**) was ruthenium in an acidic medium at 150 °C (run 39). However, the conversion in this reaction was only 5% after 21 h. The next best systems utilized ruthenium in basic media at 150 °C or greater but these were contaminated with significant amounts of neomenthol (**4**) (runs 35, 36, and 37).

Neomenthol itself was produced in 89% selectivity from menthone (82% overall of all four diastereomers) by the use of rhodium in 0.6 N HCl at 105 °C (run 49). Conversion was excellent, 98% in 20 h.

Surprisingly, raising the temperature to 150 °C prevented the latter reaction from proceeding at all (run 50). This observation was repeated a number of times interspersed with successful runs at 105 °C to verify that fact that it was a valid observation. Additional cases of drastically reduced reaction rates as a result of increasing the temperature from 105 to 150 °C when working in an acidic medium were also observed with the ruthenium (run 38 vs. run 39) and platinum (run 64 vs. run 65) catalysts.

Platinum on carbon was also highly effective in favoring production of **4** over **3** when the hydrogenation was carried out in aqueous HCl (runs 62–65), although not to the degree of rhodium.

The hydrogenation of isomenthone (**2**) was generally more stereoselective than the hydrogenation of menthone (**1**) with all of these catalysts. Depending on conditions, **2** could be

Table III. Hydrogenation of Menthone-Isomenthone in Neutral Media

Run no.	Medium	Metal	Temp, °C	Press, psig	Product distribution, % 3	4	5	6	3 + 4	time, h	Conversion, %
31	H_2O	Ru	105	100	21	49	9	21	70	2.25	90
32	H_2O	Ru	150	100	46	29	23	2	75	20	96
33	H_2O	Ru	150	500	46	24	26	4	70	23	96
40	EtOH	Ru	105	100	19	41	7	33	60	45	95
41	H_2O	Rh	105	75	Very little reaction					28	
51	EtOH	Rh	105	200	No reaction					22	
53	H_2O	Pt	105	100	25	55	0.5	19.5	80	22	81
54	H_2O	Pt	150	100	43	38	4	15	81	22	78
55	H_2O	Pt	105	400	33	41	1	25	74	22	96
56	H_2O	Pt	150	400	34	41	2	23	75	20	93

Table IV. Hydrogenation of Menthone-Isomenthone in Basic Media

Run no.	Medium	Metal	Temp, °C	Press, psig	Product distribution, % 3	4	5	6	3 + 4	Time, h	Conversion, %
34	0.6 M NaOH	Ru	105	100	24	41	13	22	65	4.5	98
35	0.6 M NaOH	Ru	150	100	57	26	16	1	83	16	90
36	0.6 M NaOH	Ru	190	300	60	27	12	1	87	18	92
37	1.25 M NaOH	Ru	150	100	48	35	16	1	83	6.5	34
42	0.6 M NaOH	Rh	105	75	28	48	5	19	76	15	87
43	0.6 M NaOH	Rh	105	150	25	52	4	19	82	5.3	49
44	0.6 M NaOH	Rh	150	75	45	35	11	9	80	18	82
45	1.25 M NaOH	Rh	105	75	27	52	6	15	79	28	99
46	1.25 M NaOH	Rh	150	100	50	36	12	2	86	20	97
47	1.25 M NaOH	Rh	150	500	37	49	8	6	86	6.5	99
48	5.0 M NaOH	Rh	150	100	54	31	13	1	85	21	97
52	0.6 M Bu_4NOH	Rh	105	75	30	51	0	19	81	18	13
57	0.6 M NaOH	Pt	105	100	32	53	1	14	85	21	100
58	0.6 M NaOH	Pt	150	100	46	47	2	5	93	6.5	95
59	0.6 M NaOH	Pt	105	500	28	52	0.5	19.5	80	21	100
60	0.6 M NaOH	Pt	150	500	37	53	1	9	90	19	98
61	0.6 M NaOH	Pt	190	300	44	46	3	7	90	6.5	100

Table V. Hydrogenation of Menthone-Isomenthone in Acidic Media

Run no.	Medium	Metal	Temp, °C	Press, psig	Product distribution, % 3	4	5	6	3 + 4	Time, h	Conversion, %
38	0.6 M HCl	Ru	105	100	21	44	5	30	65	19	34
39	0.6 M HCl	Ru	150	100	67	19	8	6	83	21	5
49	0.6 M HCl	Rh	105	100	10	82	1	7	92	20	98
50	0.6 M HCl	Rh	150	100	No reaction					25	
62	0.6 M HCl	Pt	105	400	24	65	0	11	89	6	100
63	0.6 M HCl	Pt	150	400	17	75	0	8	92	20	96
64	0.6 M HCl	Pt	105	100	19	68	1	12	87	3	100
65	0.6 M HCl	Pt	150	100	43	51	1	5	94	5	56

converted to either **5** or **6**. With ruthenium, under either neutral or basic conditions, **5** was produced from **2** in 87–94% selectivity so long as the temperature was 150 °C. At 105 °C, **6** predominated. This represents a remarkable shift in selectivity for a difference of 45 °C in reaction temperature (runs 31–33 and 34–37).

For the synthesis of **6** from **2**, platinum was generally the most selective under all conditions, especially those of runs 55, 56, 59, 60, and 62–64.

One interesting comparison was the substitution of the tetraalkylammonium ion, Bu_4N^+ (run 52), for Na^+ (run 42) under otherwise identical conditions. The tetrabutylammonium ion slowed the rate of reaction considerably and affected the product distribution mainly by increasing the total of **3** + **4** from 76% to 81% and by completely eliminating the formation of **5**.

In examining the product distribution in terms of products (**3** and **4**) derived from menthone and those (**5** and **6**) from isomenthone, it is clear that the experimentally determined distribution does not reflect that of the starting ketone mixture. The total **3** + **4** usually exceeds 70% (the percentage of **1** in the starting material) and often by a large amount (**3** + **4** = 94% in one case).

This reflects the fact that the catalysts are generally more selective to the hydrogenation of menthone than isomenthone and that ketone epimerization is able to compete with hydrogenation. Thus, as **1** is reduced to the alcohols **3** and **4**, additional **1** is created from **2** via the tendency of the equilibrium between **1** and **2** to reestablish itself. Proof of this was obtained via examination of the ratio of residual **1** and **2** after workup of some of the reactions. The amount of **1** never exceeded 70% and was usually in the range of 55–69%.

Four interesting exceptions to the generality of **5** + **6** <30% are found in runs 34, 38, 40, and 42. All of these were run at 105 °C and low pressure. In these cases the rate of reaction of **2** must be greater than that of **1** by at least 70/30. If the rate of

epimerization of **2** is not rapid, one might hope to utilize the conditions of runs 38, 40, and 42 in a highly selective (83–86%) synthesis of **6**, given a source of pure **2**.

During the course of our work and in the results and discussion presented above we have treated the formation of the pair **3** + **4** and the pair **5** + **6** as arising exclusively from the respective precursors **1** and **2** as shown in Scheme I. Since **1** and **2** are undoubtedly in dynamic equilibrium under reaction conditions, we have chosen to represent the synthesis, say of **3** + **4** from **2** as occurring only through prior equilibrium of **2** to **1**. The result of this assumption is that the ratio of **3** and **4** to each other represents the true product distribution in the hydrogenation of **1**.

This assumption ignores the very real possibility that an enolic form of the substrates may be involved in the reaction pathway. However, we did not explore this matter further as the effects of acid and base on heterogeneous ketone hydrogenation catalysts appear to be poorly understood.[1g]

Experimental Section

Representative reactions are given here. Solvents were all commercially available anhydrous or absolute grades. Lithium metal was purchased from Lithium Corp. as wire of 42.3 mg/cm.[7] Sodium and potassium were purchased from Fisher Scientific and cut into small hunks under hydrocarbon solvent. The analytical GC column, Carbowax 400, was supplied by D. G. Gillen.[3] We have tested a number of samples of this column and have found reproducibility to be excellent. Care should be exercised in that it is extremely sensitive to destruction by oxygen.

All hydrogenations at less than 200 psig were performed in 3-oz glass Fischer-Porter aerosol compatibility tubes. Solutions were stirred magnetically and hydrogen was supplied from a reservoir via a pressure regulator. Those reductions at greater than 200 psig were performed in a stirred 300-ml autoclave except for the acid runs 32 and 33, which were performed in special nickel-clad Fischer-Porter tubes.[8] Rh on carbon (5%) was purchased from Matthey-Bishop, Inc.; 5% Ru on carbon and 5% Pt on carbon were purchased from Engelhard Industries. An equilibrium mixture (70/30) of menthone–isomenthone was purchased from Columbia Organic Chemicals Co.

Reduction of Menthone–Isomenthone in Liquid Ammonia. Into a nitrogen-flushed 500-ml flask fitted with NH_3 condenser and nitrogen head, dry ice–acetone cooling bath, and magnetic stirrer were placed a 98.6:1.4 mixture[4] of menthone and isomenthone (3.0 g, 19 mmol), ethanol (32 ml), and ether (18 ml). Approximately 125 ml of NH_3 was condensed in from a lecture bottle and then lithium wire (64 cm, 2.7 g, 39 g-atom) was added in 1–2-cm lengths over 30 min. The mixture was stirred cold until the blue color disappeared, then NH_3 was allowed to evaporate overnight. Water (175 ml) and then concentrated HCl (to pH 2) were added and the mixture was extracted three times with 60 ml of ether. The ether layers were combined, dried with $MgSO_4$, filtered, and concentrated to afford product. Gas chromatography revealed no ketone, 98.6% menthol, and 1.4% isomenthol.

Reduction of Menthone–Isomenthone with Sodium in Wet Ether. Into a nitrogen-flushed 100-ml flask fitted with reflux condenser and nitrogen head, stirrer, and low-temperature thermometer were placed ether (50 ml), water (0.5 ml, 28 mmol), and ketone mix (98.6:1.4 menthone–isomenthone, 3.35 g, 22 mmol). This mixture was cooled with an ice–salt bath to −2.5 °C. Sodium (1.2 ml, 1.15 g, 50 mmol) was added in small pieces over 10 min and the reaction mixture was stirred at approximately 4 °C for 2 h. The metal-free solution was then mixed with water, shaken, and separated, and the organic layer was concentrated on a rotary evaporator. The resulting oil was then dissolved in a minimal amount of ethanol and analyzed by GC which revealed less than 1% menthone and isomenthone; 99+% menthols in the ratio 3% neomenthol:2% neoisomenthol:87.5% menthol:7.5% isomenthol.

Reduction of Menthone–Isomenthone with Platinum on Carbon. Into a 3-oz Fischer-Porter tube containing a magnetic stir bar were placed menthone–isomenthone mix (3.0 g, 19 mmol), 5% Pt/C (100 mg), and 0.6 N HCl (10 ml). The tube was placed on the hydrogenation manifold, pressurized to 100 psig H_2, and surrounded by a 105 °C oil bath mounted on a magnetic stirrer. The reaction mixture was stirred for 3 h with the reactor pressure maintained at 100 psig. The system was then cooled and vented, and the mixture was filtered through Celite and washed through with ether (15 ml). The combined filtrates were shaken and separated and the organic layer dried with $MgSO_4$, filtered, and concentrated. Gas chromatographic analysis revealed a mixture of >99.5% diastereomeric menthols (19% **3**, 68% **4**, 1% **5**, 12% **6**) and <0.5% residual ketones.

Reduction of Menthone–Isomenthone with Ruthenium on Carbon. Into a 3-oz Fischer-Porter tube containing a magnetic stir bar were placed menthone–isomenthone mix (3.0 g, 19 mmol), 5% Ru/C (100 mg), and distilled water (7 ml). The tube was placed on the hydrogenation manifold, pressurized to 100 psig, and surrounded by a 105 °C oil bath mounted on a magnetic stirrer. The reaction mixture was stirred for 2.25 h, cooled, vented, and filtered through Celite. After the Celite was washed through with ether (15 ml) the combined filtrates were shaken and separated. The organic layer was dried with $MgSO_4$, filtered, and concentrated. Gas chromatographic analysis revealed the presence of 90% diastereomeric menthols (21% **3**, 49% **4**, 9% **5**, and 21% **6**) and 10% residual ketones (70% **1** and 30% **2**).

Reduction of Menthone–Isomenthone with Rhodium on Carbon. Into a 3-oz Fischer-Porter tube containing a magnetic stir bar were placed menthone–isomenthone mix (3.5 g, 23 mmol), 5% Rh/C (105 mg), and 0.6 M NaOH (7 ml). The tube was placed on the hydrogenation manifold, pressurized to 75 psig, and surrounded by a 105 °C oil bath mounted on a magnetic stirrer. The mixture was stirred for 15 h, cooled, vented, and filtered through Celite. After the Celite was washed through with ether (15 ml) the combined filtrates were shaken and separated. The organic layer was dried with $MgSO_4$, filtered, and concentrated. Gas chromatographic analysis revealed a mixture of 87% diastereomeric menthols (28% **3**, 48% **4**, 5% **5**, and 19% **6**) and 13% residual ketones (64% **1** and 36% **2**).

Registry No.—**1**, 89-80-5; **2**, 491-07-6; ammonia, 7664-41-7; sodium, 7440-23-5; platinum, 7440-06-4; ruthenium, 7440-18-8; rhodium, 7440-16-6; K, 7440-09-7.

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(3) D. G. Gillen and J. T. Scanlon, *J. Chromatogr. Sci.*, **10**, 729 (1972).

(4) In actual practice, pure menthone is very difficult to obtain. We synthesized our 98.6:1.4 ratio material by oxidation of *dl*-menthol according to the procedure of H. C. Brown, C. P. Garg, and K-T. Liu, *J. Org. Chem.*, **36**, 387 (1971). An alternate procedure would be the slow equilibrative distillation of menthone from a menthone–isomenthone mixture by the technique of Barney and Hass (cf. ref 2m).

(5) Based on the method for cycloalkanone reduction discussed by J. W. Huffman and J. T. Charles, *J. Am. Chem. Soc.*, **90**, 6486 (1968), and W. S. Murphy and D. F. Sullivan, *J. Chem. Soc., Perkin Trans. 1*, 999 (1972), and references cited therein.

(6) Under the reaction conditions employed, the initially formed product distribution most likely is identical with the final product distribution observed, i.e., diastereomeric isomerization of products does not occur. The conditions necessary for such diastereomeric isomerization are generally much more rigorous than those employed here (cf. ref 1).

(7) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Wiley, New York, N.Y., 1967, p 570.

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Synthesis of β,γ-Unsaturated Aromatic Hydrocarbons by Tandem Phenylation–Reduction of α,β-Unsaturated Aldehydes and Ketones. Product Prediction and Synthetic Utility[1]

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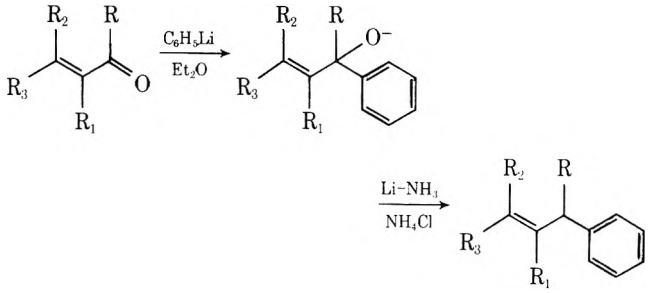
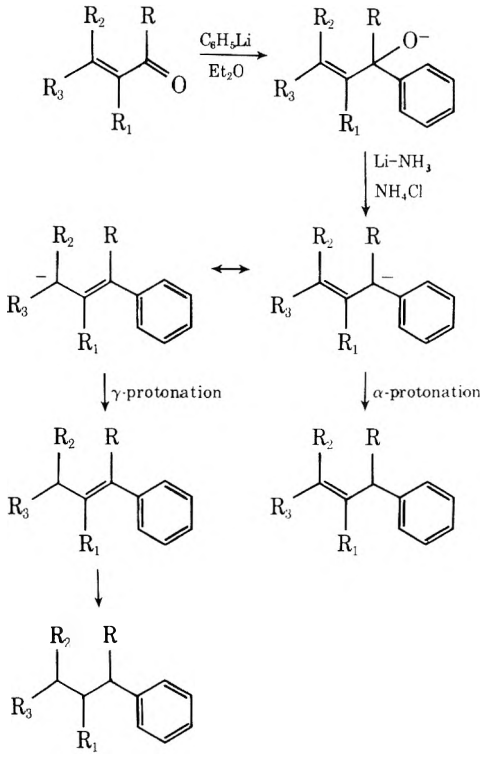
Based on 15 α,β-unsaturated aldehydes and ketones surveyed, product prediction in the tandem phenylation–reduction of such carbonyl compounds seems to be possible. If there are only hydrogens at the β position of the α,β-unsaturated system the product is the corresponding aromatic hydrocarbon. All other alkyl-substituted α,β-unsaturated aldehydes yield the corresponding β,γ-unsaturated aromatic hydrocarbons. Alkyl-substituted α,β-unsaturated ketones are less predictable and sometimes result in mixtures. Consequently, on appropriate α,β-unsaturated aldehydes and ketones, this phenylation–reduction procedure is a unique method for the rapid synthesis of β,γ-unsaturated aromatic hydrocarbons and serves as a convenient alternative to tthe Wittig reaction.

This laboratory recently introduced a convenient tandem phenylation–reduction procedure for the rapid synthesis of aromatic hydrocarbons from aldehydes and ketones.[3] The sequence involves the lithium–ammonia–ammonium chloride reduction of a benzyl alkoxide that is generated in situ by phenylation of the carbonyl system. Included in this study



were a few α,β-unsaturated aldehydes and ketones that generally yielded the corresponding β,γ-unsaturated aromatic hydrocarbon. Such a product indicates that in the reduction of the benzyl alkoxide[4] (see Scheme I) the intermediate anion

Scheme I



protonates exclusively at the benzylic position (α-protonation) forming the β,γ-unsaturated aromatic hydrocarbon that survives in statu quo. However, in a few cases, the corresponding saturated aromatic hydrocarbon was also formed indicating that some protonation occurred at the allylic position (γ-protonation) yielding the styrene system that would be rapidly reduced[5] to the aromatic hydrocarbon. The purpose of our present study was to survey a reasonable sampling of α,β-unsaturated aldehydes and ketones to establish the structural or substituent requirements that might enable product prediction and at the same time explore the synthetic utility of the method.

The general procedure is to genneerate a benzyl alkoxide in a metal–ammonia reaction vessel by the addition of the α,β-unsaturated aldehyde or ketone to phenyllithium in ether. Ammonia is subsequently distilled into the vessel, and then the resultant dark blue mixture is cautiously quenched with ammonium chloride. Table I is a listing of the α,β-unsaturated carbonyl compounds that were subjected to these phenylation–reduction conditions with the results. Eight of the α,β-unsaturated aldehydes (**3, 4, 5, 6,** and **7**) and ketones (**9, 10,** and **14**) yielded only the corresponding β,γ-unsaturated aromatic hydrocarbon indicating exclusive protonation at the benzylic position (α-protonation). In contrast, three of the α,β-unsaturated carbonyl compounds (**1, 2,** and **8**) yielded the corresponding aromatic hydrocarbon as the sole product. The aromatic hydrocarbon product is the result of protonation at the primary allylic anion position (γ-protonation) followed by the rapid metal–ammonia reduction of the styrene system.

Only with three α,β-unsaturated ketones (**11, 12,** and **13**) studied did mixtures result. The presence of an alkyl group (R = alkyl) at the benzylic position, after phenylation of the α,β-unsaturated ketones, introducedd the possibility of steric hindrance to protonation[6] of the intermediate anion at this carbon (α-protonation) and consequently some protonation at the allylic position (γ-protonation) is observed. This effect, however, can be very subtle. Compare, for example, (+)-pulegone (**10**) with piperitone (**11**) and (−)-carvone (**12**). Steric effects can also play an important role in protonation at the allylic position. The intermediate anion from the phenylation–reduction of ketone **13** protonates at both positions while with α-ionone (**14**) the introduction of the three neighboring methyll groups in the ring protects the γ position and only α-protonation is detected. With β-ionone (**15**) it is impossible to determine whether the protonation occurred at the α site or at both the α and γ site since the resultant olefin from either would reduce to **30**.[7] Protonation at the allylic anion position leaves a vulnerable styrene system and protonation at the benzylic position, which seems reasonable by analogy to α-

Table I. Phenylation–Reduction of α,β-Unsaturated Aldehydes and Ketones

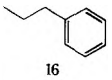
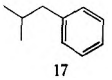
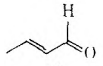
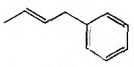
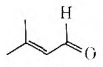
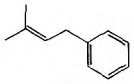
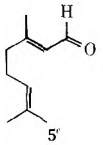
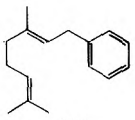
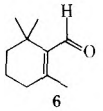
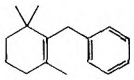
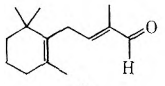
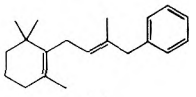
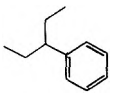
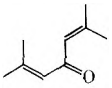
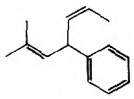
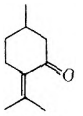
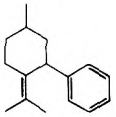
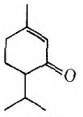
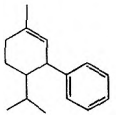
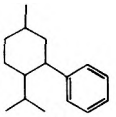
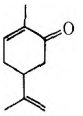
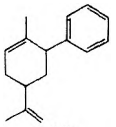
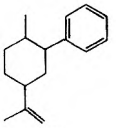
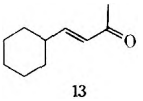
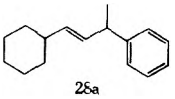
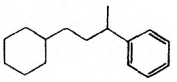
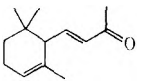
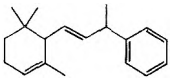
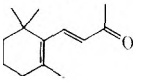
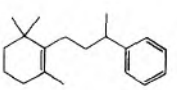
α,β-Unsaturated carbonyl compd	Product(s)		Yield	
	α-Protonation	γ-Protonation	Small scale[a] anal[c]/isol[d]	Large scale[b] anal[c]/isol[d]
 1		 16	100/94	
 2		 17	95/86	
 3	 18		92/86	96/94
 4	 19		98/95	98/94
 5[e]	 20[f]		100/90	99/94
 6	 21[f]		100/99	95/90
 7	 22[f]		99/93	99[g]/97
 8		 23	99/97	
 9	 24[f]		93/93	
 10[h]	 25[f]		98/85	
 11	 26a	 26b	83[i]/80	
 12[f]	 27a	 27b	100[k]/98	
 13	 28a	 28b	99[l]/94	
 14	 29		99/95	
 15		 30[f,m]	100/98	

Table I (*Footnotes*)

[a] Small scale reaction using 2.5 mmol of carbonyl compound. See the Experimental Section for details. [b] In this and previous studies, the reactions were performed on a small scale and for mechanistic reasons with a large excess of lithium. Included in this work are the optimal conditions for a scaled-up synthesis (25 mmol) using the minimal amount of lithium. See Experimental Section for details. [c] Analyzed by GLC (% of volatiles). [d] Isolated by column chromatography. [e] The aldehyde was a commercial sample of citral. [f] See ref 3 for the spectral data, composition analysis, and any special experimental comments or instructions. [g] The large scale reaction required 1.58 g (230 mg-atoms) of lithium. [h] Sample was (+)-pulegone. [i] Mixture (60:40) of **26a** and **26b**. [j] Sample was (−)-carvone. [k] Mixture (65:35) of **27a** and **27b**. [l] Mixture (65:35) of **28a** and **28b**. [m] May have been formed by either α-protonation or α- and γ-protonation. See discussion.

ionone (**14**), would leave a 1,3-diene system that would reduce to the olefin **30** by 1,2 addition to the less substituted double bond.

In summary, product prediction in the tandem phenylation–reduction of α,β-unsaturated aldehydes and ketones seems to be possible. If there are *only* hydrogens at the β position of the α,β-unsaturated system the product will be the corresponding aromatic hydrocarbon. All other alkyl substituted α,β-unsaturated aldehydes should yield the correesponding β,γ-unsaturated aromatic hydrocarbons. Only the alkyl substituted α,β-unsaturated ketones are less predictable and can result in mixtures that are difficult to separate.[8] Consequently this phenylation–reduction procedure, when used on appropriate α,β-unsaturated aldehydes and ketones, is a uniquely simple method for the rapid synthesis of β,γ-unsaturated aromatic hydrocarbons and serves as a convenient alternative to the Wittig reaction.[9]

Experimental Section[10]

General Comments. See ref 3 for general experimental comments. Gas chromatography (GLC) analyses were performed on 100 × 0.4 cm (i.d.) glass columns packed either with 4% silicon gum rubber UCC-W-982 (methylvinyl) supported on 80–100 mesh HP Chromosorb W (AW, DMCS) or with 3% silicon gum rubber OV-17 (methylphenyl) supported on 80–100 mesh HP Chromosorb W. Purification of the product by column chromatography was accomplished on chromatographic grade activated alumina (80–325 mesh, Matheson Coleman and Bell) by elution with petroleum ether. Evaporative distillations, sometimes necessary for microanalyses, were performed in a Kügelrohr oven. The assigned structure of each product (or mixture) was consistent with the spectral data and composition analysis. Significant spectral data on all new compounds are included in the Experimental Section. The phenylation–reduction of 3-methyl-2-butenal (**4**) is described, in detail, to illustrate the small-scale reaction; and (*E*)-2-butenal (**3**) to illustrate the large-scale reaction.

Phenylation–Reduction of 3-Methyl-2-butenal (4). 3-Methyl-1-phenyl-2-butene (19, Small Scale). To a metal–ammonia reaction vessel containing a stirred mixture of 280 mg (40.0 mg-atoms, ca. 25 pieces) of lithium foil in 10 ml of anhydrous ether was slowly added a solution of 790 mg (5.00 mmol) of bromobenzene in 7 ml of ether. After 1 h a solution of 210 mg (2.500 mmol) of 3-methyl-2-butenal (**4**) in 8 ml of ether was slowly added and the mixture was stirred for an additional 1 h. Ammonia (ca. 25 ml) was carefully distilled[11] into the mixture and, once the dark blue color of the mixture was established,[12] ca. 3 g of ammonium chloride was cautiously added[13] (ca. 5 min) to discharge the blue color and then the ammonia was allowed to evaporate. After the residue had been partitioned between brine and ether, the organic phase was dried ($MgSO_4$), filtered, concentrated at water aspirator pressure, and then analyzed (GLC). Following column chromatography 323 mg (95%) of 3-methyl-1-phenyl-2-butene (**19**) was obtained as a colorless oil: ir (film) 3080, 3060, 3025, 2965, 2910, 1600, 1490, 1450, 1370, 730, 690 cm^{-1}; NMR (60 MHz, CCl_4) δ 7.20 (5 H, apparent s), 5.40 (1 H, t with fine splitting, J = 7.5 and 1.5 Hz), 3.31 (2 H, d, J = 7.5 Hz), and two overlapping doublets at 1.74 (3 H, d, J = 1.5 Hz) and 1.69 (3 H, d, J = 1.5 Hz); mass spectrum m/e (rel intensity) 146 (M^+, 52), 131 (100), 91 (68), 77 (11).

Anal. Calcd for $C_{11}H_{14}$: C, 90.35; H, 9.65. Found: C, 90.37; H, 9.53.

Phenylation–Reduction of (*E*)-2-Butenal (3). (*E*)-1-Phenyl-2-butene (18, Large Scale). To a metal–ammonia reaction vessel containing a stirred mixture of 1.05 g (150 mg-atoms, ca. 50 pieces) of lithium foil in 25 ml of anhydrous ether was slowly added (ca. 10 min)[14] a solution of 5.84 g (37.0 mmol) of bromobenzene in 25 ml of ether. After 50 min, the reaction mixture was diluted with 50 ml of ether and then cooled[15] to ca. −70 °C (dry ice–acetone bath). A solution of 1.75 g (25.0 mmol) of (*E*)-2-butenal[16] in 25 ml of ether was slowly added (ca. 15 min) and after 10 min the cooling bath was removed and the mixture stirred for 50 min. After a further dilution with 75 ml of ether, ca. 200 ml of ammonia was carefully distilled[11] (30–40 min) into the mixture and after 10 min the dark blue color of the reaction mixture was discharged by the addition[13] (ca. 20 min) of excess ammonium chloride (ca. 7 g). After the ammonia had evaporated the residue was partitioned betwween ether and brine. The organic phase was dried ($MgSO_4$), filtered, concentrated at water aspirator pressure, and then analyzed (GLC). Following column chromatography 3.10 g (94%) of (*E*)-1-phenyl-2-butene (**18**) was obtained as a colorless oil: bp 110–121 °C (760 Torr); $n^{24}D$ 1.5120; ir (film) 3090, 3070, 3035, 2965, 2925, 1605, 1495, 1450, 965, 740, 690 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 7.14 (5 H, apparent s), 5.72–5.26 (2 H, m), 3.26 (2 H, d, J = 4.9 Hz), 1.64 (3 H, d, J = 4.6 Hz); mass spectrum m/e (rel intensity) 132 (M^+, 55), 117 (100), 91 (65).

Anal. Calcd for $C_{10}H_{12}$: C, 90.85; H, 9.15. Found: C, 90.68; H, 9.21.

(*E*)-1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-3-phenyl-1-butene (29). Ir (film) 3080, 3055, 3020, 2955, 2915, 2860, 1600, 1490, 1445, 1375, 1370, 1360, 965, 750, 690 cm^{-1}; NMR (60 MHz, CCl_4) δ 7.22 (5 H, s), two quartets centered at 5.67 (1 H, q, J = 16 and 6 Hz), and 5.25 (1 H, q, J = 16 and 8 Hz) on which is superimposed a multiplet at 5.53–5.26 (1 H, m), 3.45 (1 H, broad quintet, J = ca. 7 Hz), 2.25–1.69 (3 H, broad m), 1.69–1.50 (3 H, m), 1.34 (3 H, sharp d, J = 7.2 Hz) superimposed on a multiplet at 1.50–1.09 (2 H, m), and four singlets at 0.90, 0.88, 0.86, and 0.82 (6 H, two conformers); mass spectrum m/e (rel intensity) 254 (M^+, 15), 239 (4), 197 (96), 183 (40), 105 (85), 93 (100), 91 (94), 77 (83), 69 (32).

Anal. Calcd for $C_{19}H_{26}$: C, 89.70; H, 10.30. Found: C, 89.84; H, 10.15.

Acknowledgments. The authors wish to thank Dr. F. Scheidl, Hoffmann-La Roche Inc., Nutley, N.J., for the microanalyses.

Registry No.—**1**, 107-02-8; **2**, 78-85-3; **3**, 123-73-9; **4**, 107-86-8; **5**, 141-27-5; **6**, 432-25-7; **7**, 14398-40-4; **8**, 1629-58-9; **9**, 504-20-1; **10**, 89-82-7; **11**, 89-81-6; **12**, 6585-40-1; **13**, 41437-84-7; **14**, 127-41-3; **15**, *14901-07-6*; **18**, *935-00-2*; **19**, *4489-84-3*; **29**, *59939-06-9*.

References and Notes

(1) Part 8 in the series "Alkylation–Reduction of Carbonyl Systems". For part 7 see S. S. Hall, C.-K. Sha, and F. Jordan, *J. Org. Chem.*, **41**, 1494 (1976).
(2) Taken in part from the Ph.D. Thesis of F. J. M. and the M.S. Thesis of C.-K.S., Rutgers University, 1975.
(3) S. S. Hall and F. J. McEnroe, *J. Org. Chem.*, **40**, 271 (1975).
(4) For a discussion of the proposed mechanism of the reduction of benzyl alkoxides to aromatic hydrocarbons see (a) S. S. Hall, S. D. Lipsky, and G. H. Small, *Tetrahedron Lett.*, 1853 (1971); (b) S. S. Hall, S. D. Lipsky, F. J. McEnroe, and A. P. Bartels, *J. Org. Chem.*, **36**, 2588 (1971).
(5) W. Hückel and H. Bretschneider, *Justus Liebigs Ann. Chem.*, **540**, 157 (1939).
(6) A contributing factor, of course, could be that the benzylic position is a tertiary carbanion with the ketones and secondary with the aldehydes, but we feel that this is not dominating. Compare, for example, the results of ketone **13** with **14**.
(7) The phenylation–reduction of this ketone has been previously discussed in ref 3 and includes the results of some mechanistically informative experiments.
(8) These considerations do not apply to aromatic substituents on the α,β-unsaturated aldehydes and ketones. See S. S. Hall, *J. Org. Chem.*, **38**, 1738 (1973).
(9) A. Maercker, *Org. React.*, **14**, 270 (1965).
(10) GLC analyses were determined on a Hewlett-Packard Model 7610A (flame detector) chromatograph. The ir spectra were determined with a Beckman Model IR-10 or Model AccuLab 6 infrared recording spectrophotometer. The ^1H NMR spectra were determined at 60 MHz with a Varian Associates Model A-60 NMR spectrometer and at 100 MHz with a JEOL Model JNM-PS-FT-100 fast Fourier transform NMR spectrometer. The chemical shifts are expressed in δ values (parts per million) relative to a Me_4Si internal standard. The mass spectra were determined with an AEI Model MS-30

mass spectrometer (70 eV) to which was interfaced a Pye Unicam Model 104 gas chromotograph. The refractive indexes were determined with a Bausch and Lomb refractometer.

(11) To increase the efficiency of the condensation process, the reaction vessel was cooled (dry ice–acetone bath); and to prevent splattering, the apparatus was tilted slightly to allow the condensing ammonia to run down the walls of the flask.

(12) Normally ca. 10 min elapsed before proceeding with the quenching step, although the time interval does not seem critical.

(13) The NH_4Cl is most conveniently introduced by attaching a glass bulb filled with the salt to a side arm by means of tygon tubing. When the NH_4Cl is to be added, the bulb is raised and tapped gently to smoothly introduce the quenching agent. Should this step start to become violent, the addition and sometimes even the vigorous stirring should be momentarily stopped to avoid an eruption.

(14) During the addition the exothermic reaction was moderated (25–30 °C, internal thermometer) with a water bath.

(15) The temperature was lowered as a precaution to minimize the possibility of competing side reactions. See J. D. Buhler, *J. Org. Chem.*, **38**, 904 (1973).

(16) (*E*)-2-Butenal (crotonaldehyde), which is stabilized with 10% water, was distilled, bp 95–100 °C (760 Torr), just prior to use.

Diels–Alder Reactions of *o*-Benzoquinones. A Route to Derivatives of Δ^2-1-Octalone

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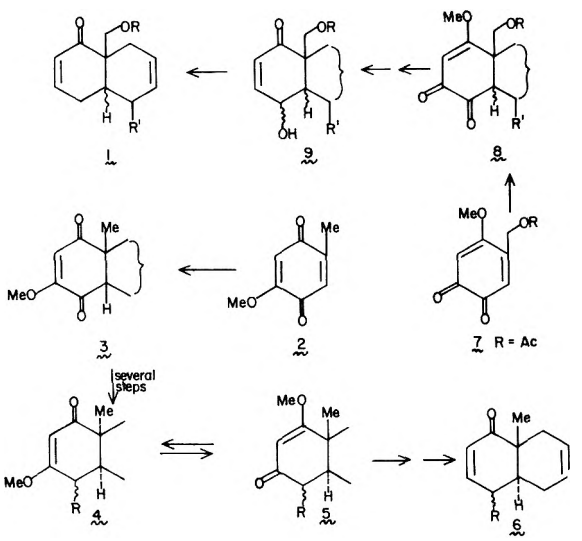
Received April 13, 1976

Diels–Alder reactions of 4-methoxy-5-acetoxymethyl-1,2-benzoquinone (**7**) and 4-methoxy-5-methoxymethyl-1,2-benzoquinone (**40**) have been shown to occur smoothly with acyclic dienes. In all cases, cycloaddition occurs at the 5,6 rather than 3,4 double bond. With 1-methoxybutadiene as the diene, regiospecific formation of the 8- rather than 5-methoxy isomer is observed. The applicability of stereospecific "endo" addition has been demonstrated. The adducts produced can be converted in five steps to angularly (**8a**) substituted derivatives of 4a,5,8,8a-tetrahydronaphthalen-1(4*H*)-one.

As part of a synthetic study directed at various elemanolide sesquiterpenoids, we had need to develop a simplified route to angularly functionalized hexalones of the type **1**. The known route to such systems, in the angular methyl series, involved equilibration of β-methoxyenones such as **4** with their vinylogous isomers, **5**.[1,2] Reduction affords a β-methoxyallylic alcohol which is unravelled with acid to give **6**.[3,4] System **4** is obtained by the Woodward route,[5] which starts with a Diels–Alder cycloaddition of methoxytoluoquinone **2** with 1,3-butadiene. The cis adduct **3** is epimerized to the trans series, and the C_4 ketone is selectively reduced to give an alcohol.[1] Interconversion of **4** with **5** has been achieved either on the derived tosylate, **4** (R = OTs),[2] or on the reduction product thereof, **4** (R = H). Alternatively the β-diketone, derived from hydrolysis of **4** (R = H), has been converted to a mixture of **4** and **5** (R = H).[1]



Since the stability of **4** vs. **5** is apparently a sensitive and unpredictable function of the nature of the substituents, we preferred to develop an entry to **1** in which such a process is not necessary. If, instead of a *p*-quinone, an *o*-quinone such as **7** is used as the dienophile, an adduct of the type **8** would be produced. Reduction of both carbonyl groups followed by the same type of acidic transformation which is involved in the conversion of **5** → **6** would provide **9** from **8**. Reductive transformation of **9** → **1** could easily be envisaged.

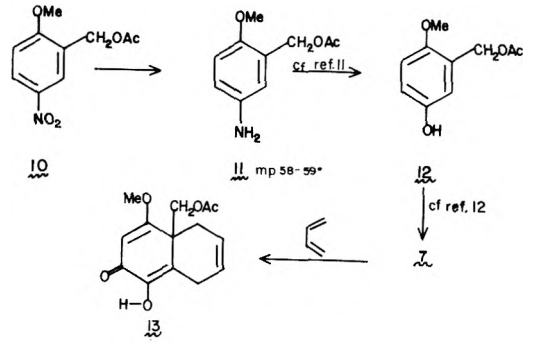
Prior to this investigation, the use of o-quinones as dienophiles had received relatively little attention. Of course, Gates and co-workers had utilized a 1,2-napthoquinone as a dienophile in their well-known synthesis of morphine.[6] Ansell had shown[7] that activated *o*-benzoquinones, bearing a 4-cyano or 4-carbomethoxy substituent, were sufficiently activated to react as dienophiles with reactive acyclic dienes such as 2,3-dimethylbutadiene. Subsequent work demonstrated that with simple, nonactivated *o*-quinones,[8] only with massive excesses of 2,3-dimethylbutadiene could Diels–Alder adducts be obtained. Horspool had concluded[9] that the propensity for dimerization and decomposition of simple o-quinones is such that Diels–Alder reaction with unactivated dienes was apparently not possible.

We expected that the enophilic powers of a 4-methoxy-o-quinone should be sharply reduced since cycloaddition would necessitate dissipation of the vinylogous ester resonance of the starting material. That such an effect is likely to be important is suggested by the specific dienophilicity of the 5,6 rather than 2,3 double bond of *p*-quinone **2**.[5] Furthermore, Ansell had shown that 4-methoxy-1,2-benzoquinone reacts with 2,3-dimethylbutadiene exclusively at the 5,6 rather than the 3,4 double bond,[8] presumably for the same reason. If the *enophilicity* of a system such as **7** is diminished in line with the curtailment of its *dienophilicity* at the 3,4 double bond, the possibilities of realizing cycloaddition reactions of the 5,6 double bond with a wide variety of dienes becomes more promising. This expectation has been realized in practice.

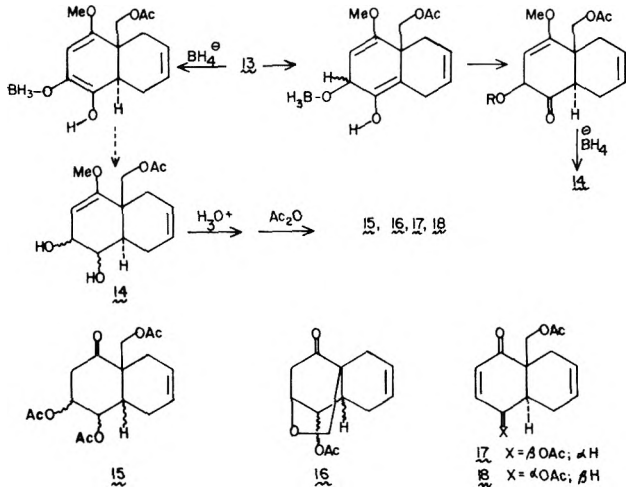
Results

The synthesis of specific compound **7** (R = OAc) started with the commercially available *p*-nitroanisole. This was

converted by known steps[10a] (chloromethylation followed by acetolysis) into the anisole derivative, **10**, and thence by steps which we have previously described into compound **7**.[10b] Heating compound **7** with 1,3-butadiene at 105 °C for 5 h gives a 63% yield of adduct **13**, mp 150–151 °C, whose structure was proven as previously described.[10b]



The existence of **13** as a diosphenol precluded systematic synthesis of both the cis- and trans-fused hexalones along the lines of the Woodward synthesis through the use of kinetic (cis) and equilbrated (trans) Diels–Alder adducts.[5] Treatment of **13** with excess sodium borohydride gave a crude tetrahydro product, **14**, which was submitted directly to the action of aqueous acid and the resultant mixture was acetylated (pyridine–Ac_2O). Chromatography of this material on silica gel



gave a mixture of keto triacetate **15** (4%), bridged ether **16** (0.50%), and the epimeric enone diacetates **17** and **18** (45% combined). While careful chromatography enabled the separation of **17** from **18** (see Experimental Section), the combined material was used for further elaboration.

Although at this point the configuration at C_{4a} was not known, subsequent transformations will show that both **17** and **18** are trans fused. The gross schematics of the sodium borohydride reduction are not known with certainty. One possibility is that reduction occurs first at C_1 through spectroscopically undetected quantities of C_1 keto tautomer. While precedent suggests that a β-methoxyenone is not reduced by sodium borohydride,[1,5] the proximity of the alkoxyborane at C_1 may facilitate intramolecular reduction at C_2. Alternatively, reduction may commence with conjugate addition to C_{8a}. While such conjugate additions to Δ^4-3-ketodecalones with sodium borohydride are not common, an accelerating effect of the hydrogen bond (in **13**) on such a reaction cannot be ruled out.

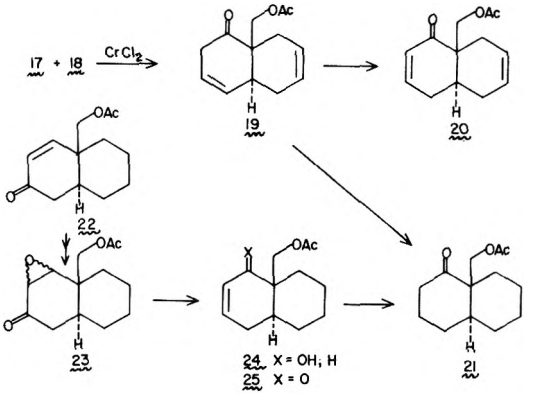
An alternative sequence starts with direct reduction at C_2 (either through a proximate alkoxyborane or because of the special accelerating effect of the diosphenol linkage). After reduction of C_2, the Δ^1-enol ketonizes and the resultant 2-hydroxy-1-ketone is further reduced with sodium borohydride to give diol **14**.

Compound **15** must be derived by competitive cleavage of the enol ether of **14** by the aqueous acid to give the 3ε,4ε-dihydroxy-1-ketone rather than Δ^2-en-1-one. The conditions for the enol ether cleavage apparently suffice to cleave the angular ester. The hydroxymethyl function cyclizes in an intramolecular Michael reaction to give **16** to a small extent. It should be noted that the junction stereochemistry in **15** and **16** has not been proven.

Reaction of the mixture of **17** and **18** with excess chromous chloride for 1 h afforded a 44% yield of β,γ-unsaturated ketone **19**. While the starting ratio of epimers was ca. 1:1, the recovered enone diacetate was virtually pure 4α-acetoxy epimer **18** (ca. 25%). These results indicate that the β epimer **17**, in which the acetoxy group is axial, is reductively cleaved by chromous chloride substantially faster than the α epimer, in which the acetoxy group is equatorial. This relative order of reductive cleavage can be rationalized on the basis of superior overlap of the departing axial acetoxy group with the π system on the enone. A similar trend has been noted in the conceptually related reductive debromination of the α-bromo ketones with zinc.[13] When **18** was resubmitted to reduction with chromous chloride, additional small amounts of **19** were obtained. Other products, which were not characterized, were noted on TLC analysis.

The isomerization of **19** → **20** was achieved (86%) by the action of aqueous HCl in THF. While the overall yield of **20** from **13** is only 15%, the directness of the method and the feasibility of entering the trans series via a Diels–Alder reaction, without recourse to cis → trans epimerization, are attractive features of the *o*-quinone route.

Catalytic hydrogenation of **19** gave a tetrahydro product, **21**. The same compound was synthesized by a five-step sequence starting with the known *trans*-acetoxymethyloctalone **22**.[14a,b] Epoxidation of **22** with alkaline hydrogen peroxide followed by acetylation with pyridine–acetic anhydride gave **23**. Treatment of **23** with hydrazine hydrate[15] afforded allylic alcohol **24** which, upon oxidation with activated MnO_2, was converted into **25**. Catalytic hydrogenation of **25** gave **21**. These transformations establish the trans stereochemistry of **21** and hence of its precursors **14**, **17**, **18**, **19**, and **20**.



With the objective of incorporating oxygen functionality into the scheme, the Diels–Alder reaction of *o*-quinone **7** with 1-methoxybutadiene was examined. On the basis of analogies discussed above, it seemed likely that cycloaddition could again occur at the 5,6 double bond. We further reasoned that of the two carbonyl groups in **7**, the C_1 center would be the more electrophilic since C_2 is part of a vinylogous ester system. Accordingly, "intial" bond formation in the cycloaddition was expected to occur between C_5 of the o-quinone and C_4 of the diene. Such an alignment would lead to adduct **27**. A similar trend was noted in our laboratory in the cycloaddition of the electronically related *p*-quinone **26** with the same diene

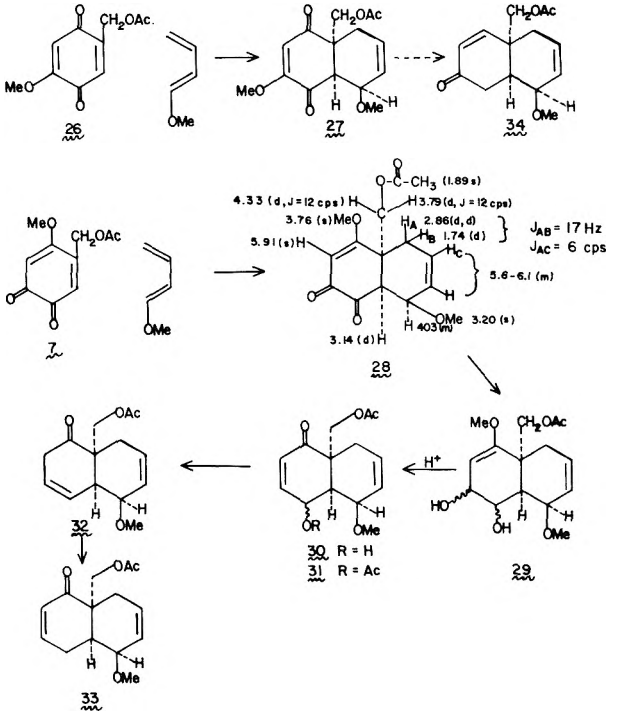
to give **27** as the sole detectable product.[14b] It will be recognized that such an alignment requires "initial" bond formation between the termini of the diene and the *more hindered* carbon of the quinone.

Reaction of **7** with 1-methoxybutadiene in methanol[16] occurred quickly under reflux. After 120 min there was obtained in 81% yield a crystalline 1:1 adduct whose structure and stereochemistry correspond to structure **28**. *Unlike the case of* **13**, *this adduct exists entirely in the* α*-diketo form.* At 250 MHz ($CDCl_3$) all the protons may be assigned and are shown in the figure in parts per million (δ) from Me_4Si. Particularly noteworthy are the absence of any exchangeable hydrogens and the appearance of a doublet, δ 3.14, J = 8 Hz, which is due to the hydrogen at C_{8a} coupled to the hydrogen at C_8. The latter is seen as a multiplet, $h_{1/2}$ = 14 Hz. While the stereochemistry indicated in **28** would have been expected on the basis of the cis–endo rules governing Diels–Alder reactions,[17] the correctness of the assignment will be rigorously established.

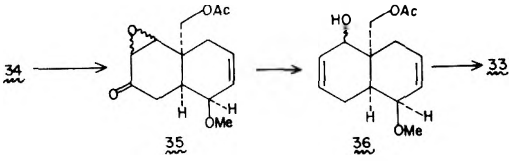
In our hands, all attempts to achieve epimerization of **28** were to no avail. Use of mild conditions ($NaHCO_3$–MeOH) gave recovery of starting material and more forcing conditions (NaOMe–MeOH) afforded intractable mixtures. Similar failures were recorded in attempted epimerizations of **27**.[14b] The definition of the structural factors which cause complete enolization in the case of **13** while exclusively favoring the α-diketone form in **28** must await further experiments with other 1-substituted butadienes.

While the 1-methoxybutadiene Diels–Alder reaction did not provide access to the trans series, a route analogous to that used to convert **13** → **20** was used with excellent success to convert **28** → **33**. *Reaction of* **28** *with sodium borohydride* gave a tetrahydro product (see discussion above for the conversion of **13** → **14**), **29**, mp 75–80 °C, which on treatment with aqueous acid gave in 97% crude recovery the alcohol **30**. Acetylation of **30** with pyridine and acetic anhydride gave (80% yield) the crystalline enone diacetate **31**, mp 81–82 °C.

Treatment of **31** with chromous chloride gave a quantitative recovery of β,γ-unsaturated isomer **32** which was isomerized with aqueous HCl–THF. The crude product was acetylated and the conjugated enone, **33**, mp 85–86 °C, was obtained in 85% yield after purification.



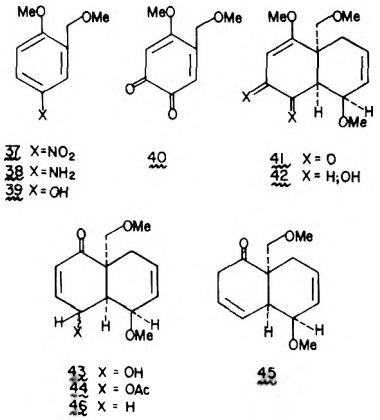
The stereochemistry of **33** (and therefore, the stereochemistry at C_{4a} and C_5 of its precursors, **28** → **32**) was confirmed by alternate synthesis. Previously[14b] we have described the synthesis of the Δ^1-3-enone **34** via the *p*-quinone Diels–Alder adduct **27** using the conventional methods of transformation. The relative stereochemistry of **34** had been established unequivocally.[14b] Epoxidation of **34** with alkaline hydrogen peroxide afforded (39%) **35**. The stereochemistry of the epoxide linkage in **35** is not known. A Wharton reaction[15] on **35** gave an allylic alcohol **36**, which, without purification, was oxidized by Corey's reagent[18] to give compound **33** (39%,



two steps). The infrared and NMR spectra as well as the melting point of **33** thus obtained were identical with those of the same compound derived from the *o*-quinone. Thus it is seen that the direct route via **7** is a considerably more expeditious pathway to **33** than is the *p*-quinone route via **26** in that no enone transposition is required.

The method was also extended to produce hexalone **46** bearing an angular methoxymethyl group. The starting material was the known[10a] 2-methoxymethyl-4-nitroanisole **37**. This was converted to the crude aniline derivative **38** and thence to the crystalline phenol **39**, mp 79–80 °C (56% for the two steps). Oxidation of **39** with Fremy's salt[12] gave a quantitative yield of *o*-quinone **40**, mp 134.5–136°C.

As before, Diels–Alder cycloaddition of **40** with 1-methoxybutadiene gave a single identifiable crystalline (76%) 1:1



adduct, mp 157.5–158.5 °C. On the basis of the strong similarity of its spectra with those of **28**, structure **41** is safely assigned to this adduct. Reduction of **41** with sodium borohydride gave a tetrahydro product **42** (100%), mp 145–145.5 °C, which, upon treatment with acid, gave a virtually quantitative yield of enone alcohol **43**. Acetylation of **43** (pyridine–acetic anhydride) gave (99%) a crystalline acetate, **44**, mp 67.5–68 °C. Reductive cleavage with chromous chloride followed by isomerization (*HCl–THF*) of *the* β,γ isomer **45** gave **46**, mp 52–53 °C (70%, two steps).

It has thus been demonstrated that 4-methoxy-*o*-quinones are viable dienophiles for Diels–Alder reactions with acyclic dienes. In this connection it must, however, be noted that we have recently found[10b] that 4-methoxy-5-methyl-1,2-benzoquinone reacts anomalously with 1,3-butadiene to give a spirodecane derivative. The definition of structural features favoring "normal" vs. "abnormal" Diels–Alder reactions of 5-alkylated 4-methoxy-1,2-benzoquinones remains to be achieved. The delineation of the structural features which favor diosphenolic (cf. **13**) as opposed to α-diketonic

(cf. 28 and 41) character in the "normal" adducts is also of importance in providing stereochemical control over the manipulation of these compounds. These issues, as well as the exploitation of the now easily accessible substitution patterns embodied in compounds **20**, **33**, and **46**, are currently being studied.

Experimental Section[19]

Reaction of 3-Methoxy-4-acetoxymethyl-1,2-benzoquinone (7) with 1,3-Butadiene. Formation of *dl*-1-Hydroxy-4-methoxy-4a-acetoxymethyl-4a,5-dihydronaphthalen-2(8*H*)-one (13). A solution of 1 g of quinone **7**,[10b] 19 ml of 1,3-butadiene, and 12 ml of benzene was heated in a sealed tube at 105 °C for 5 h. The color changed from red to light yellow. Evaporation of the volatiles left a semisolid residue which, upon trituration with ether, afforded 718 mg of **13** as a white solid. Treatment of the mother liquors with ether–hexane gave an additional 76 mg of **13** (63%): mp 150–151 °C; λ_{max} ($CHCl_3$) 3.85, 5.74, 6.15 μ; λ_{max} (EtOH) 250 (ϵ nm 10 500), 297 (2500); δ ($CDCl_3$, 250 MHz) 1.89 (s, 3), 2.18 (d, J = 18 Hz, 1), 2.30 (d, d, J = 18, 5 Hz, 1), 2.82 (br d, J = 21 Hz, 1) 3.46 (d, J = 21 Hz), 3.76 (s, 3), 4.35 (d, J = 10 Hz, 1) 4.47 (d, J = 10 Hz, 1), 5.4–6.0 (m, 3 containing a singlet at 5.72, ca. 1), 6.67 ppm (s, 1, exchangeable with D_2O); *m/e* 264 (parent).

Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.53; H, 6.04.

Direct Conversion of Compound 13 to Keto Triacetate 15, Bridged Ether 16, and Dienone Diacetates 17 and 18. To a solution of sodium borohydride (1.00 g, 0.027 mol) in 50 ml of absolute ethanol stirred at 0 °C was added adduct **13** (3.30 g, 0.0125 mol) as a solid. The system was stirred for 15 min at 0 °C and for 4 h at room temperature. The mixture was added to aqueous KCl and extracted thoroughly with chloroform. Evaporation of the volatiles left a semisolid residue which was redissolved in 25 ml of chloroform and this solution was stirred with 50 ml of 10% aqueous HCl. To the aqueous phase, after separation of the layers, was added solid KCl till saturation, and this was reextracted with chloroform. The combined chloroform layers were dried over sodium sulfate. Evaporation of the volatiles at the water pump left a residue of 2.29 g which was stirred overnight with 30 ml of acetic anhydride containing ca. 0.5 ml of pyridine. Evaporation of this solution by warming at the water pump left a residue of 2.2 g which was chromatographed on 130 g of silica gel. Elution with 4:1 hexane–ethyl acetate gave 16 mg (0.5%) of **16**, 1.57 g (45%) of a mixture of **17** and **18**, and 180 mg (4%) of **15**. Although the separation of **17** and **18** was not complete and the mixture was used in the next step, early fractions gave essentially pure **17** and later fractions gave essentially pure **18**.

For **16**: λ_{max} ($CHCl_3$) 5.81, 5.85 μ; δ ($CDCl_3$) 1.2–3.0 (m, 10 containing a singlet, ca. 3 at 2.03), 3.60 (d, J = 10 Hz, 1) 4.30 (d, J = 10 Hz, 1), 4.35 (d, d, J = 5, J_2 = 2 Hz, 1), 4.88 (d, d, J_1 = 5, J_2 = 1 Hz, 1), 5.6–5.8 ppm (m, 2); *m/e* 236 (parent).

For **17**: λ_{max} ($CHCl_3$) 5.79, 5.96 μ; δ ($CDCl_3$) 2.08 (s, 3), 2.2–2.9 (m, 8 containing a singlet, ca. 3, at 2.20), 4.2 (d, J = 12 Hz, 1), 4.75 (d, J = 12 Hz, 1), 5.5 (t, J = 5 Hz, 1), 5.6–5.8 (m, 2), 6.18 ppm (d, J = 10, 5 Hz, 1); *m/e* 278 (parent).

For **18**: λ_{max} ($CHCl_3$) 5.81, 5.96 μ; δ ($CDCl_3$) 1.8–3.0 (m, 11 containing 2, ca. 3 H singlets at 2.10 and 2.25), 4.20 (d, J = 12 Hz, 1), 4.53 (d, J = 12 Hz, 1), 5.4–5.9 (m, 3), 6.15 (d, d, J = 10, 1 Hz), 6.85 ppm (d, d, J = 10, 1 Hz, 1); *m/e* 278 (paret).

For **15**: λ_{max} ($CHCl_3$) 5.80, 5.96 μ; δ ($CDCl_3$ 2.00 (s, 3), 2.15 ppm (s, 6); *m/e* 338 (parent).

Preparation of *dl-trans*-8a-Acetoxymethyl-4a,5,8,8a-tetrahydronaphthalen-1(2*H*)-one (19). To a solution of 1.00 g (3.6 mol) of the mixture of **17** and **18** in 40 ml of acetone under an atmosphere of carbon dioxide was added 80 ml of 0.86 M aqueous chromous chloride.[20] After 1 h at room temperature, the liquid was decanted and extracted with chloroform. The chloroform extracts were dried over sodium sulfate and concentrated at the water pump to give a residue of 800 mg which was chromatographed on 40 g of silica gel. Elution with 9:1 hexane–ethyl acetate afforded 340 mg of **19** followed by 347 mg of essentially pure **18**. Resubmission of **18** to the same reaction afforded an additional 50 mg of **19** (50% combined).

19: λ_{max} ($CHCl_3$) 5.78, 5.85 μ; δ ($CDCl_3$) 2.00 (s, 3), 2.10–2.50 (m, 4), 2.5–2.7 (m, 1), 2.8–3.2 (m, 4), 4.23 (d, J = 11 Hz, 1), 4.52 (d, J = 11 Hz, 1), 5.4–6.0 ppm (m, 4); *m/e* 220 (parent).

Formation of *dl-trans*-8a-Acetoxymethyl-4a,5,8,8a-tetrahydronaphthalen-1(4*H*)-one (20). To a solution of **19** (600 mg, 2.73 mmol) in 8 ml of tetrahydrofuran was added ca. 0.2 ml of concentrated HCl. The reaction mixture was stirred at room temperature under nitrogen for 12 h. To this was added 12 ml of ether and the solution dried over anhydrous sodium sulfate. The residue, left after evaporation of the volatiles at the water pump, was chromatographed on 30 g of silica gel. Elution with 9:1 hexane–ethyl acetate afforded 515 mg (86%) of **20**: mp 38–39 °C; λ_{max} ($CHCl_3$) 5.80, 6.95 μ; δ ($CDCl_3$) 1.95 (s, 3), 2.0–2.5 (m, 7), 4.15 (d, J = 11 Hz, 1), 4.40 (d, J = 11 Hz, 1), 5.5–5.7 (m, 2), 6.0 (d, t, J_d = 10, J_t = 1 Hz), 6.8 ppm (d, t, J_d = 10, J_t = 2.3 Hz); *m/e* 220 (parent).

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 71.05; H, 7.29.

Epoxidation of 22. Formation of *dl-trans*-4a-Acetoxymethyl-3ϵ,4ϵ-oxido-3,4,4a,5,6,7,8,8a-octahydronaphthalen-2-(1*H*)-one (23). A solution of 444 mg (2 mmol) of **22**[14b] in 5 ml of methanol containing 0.6 ml of 30% aqueous hydrogen peroxide and 0.17 ml of 6 N aqueous sodium hydroxide was stirred for 3 h at room temperature. After dilution with aqueous saturated potassium chloride, the system was extracted with chloroform. The extract was dried over anhydrous sodium sulfate and concentrated at the water pump. The mixture was stirred overnight with 10 ml of acetic anhydride containing 0.5 ml of pyridine. The volatiles were removed at the water pump to afford 460 mg (97%) of **23**: λ_{max} ($CHCl_3$) 5.78, 5.84 μ; *m/e* 238 (parent).

Formation of *dl-trans*-8a-Acetoxymethyl-1ϵ-hydroxy-1,4,4a,5,6,7,8,8a-octahydronaphthalene (24). To a solution of **23** (404 mg, 1.7 mmo) in 6 ml of ethanol containing 0.02 ml of acetic acid was added 0.350 ml (7 mmol) of hydrazine hydrate. Evolution of a gas was noted. The solution was stirred for 35 min at room temperature. Dilution with water, extraction with chloroform, drying the chloroform over sodium sulfate, and evaporation of the volatiles at the water pump left a residue which was chromatographed on 27 g of silica gel. Elution with 9:1 chloroform–acetone afforded 130 mg (34%) of **24** as an oil: λ_{max} ($CHCl_3$) 2.80, 5.79 μ; *m/e* 181 (parent − 43).

Oxidation of 24. Formation of *dl-trans*-8a-Acetoxymethyl-4a,5,6,7,8,8a-hexahydronaphthalen-1(4*H*)-one (25). A solution of **24** (112 mg, 0.05 mmol) in 10 ml of chloroform was heated under reflux for 17 h with 1 g of activated manganese dioxide. The residue, obtained after filtration and evaporation of the volatiles at the water pump, was purified by preparative TLC (silica gel) using 2:1 hexane–ethyl acetate to afford 88 mg (79%) of **25**: λ_{max} ($CHCl_3$) 5.79, 5.96 μ; *m/e* 224 (parent).

Catalytic Hydrogenation of 25. Formation of *dl-trans*-8a-Acetoxymethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1(2*H*)-one (21). A solution of 18 mg of compound **25** in 1 ml of ethanol was stirred over 10 mg of 10% palladium on charcoal under 1 atm of hydrogen at room temperature for 4 h. After filtration and evaporation of the volatiles at the water pump, the residue (18 mg) was purified by preparative TLC using 2:1 hexane–ethyl acetate for elution to give 14 mg (78%) of **21**: λ_{max} ($CHCl_3$) 5.79, 5.84 μ; δ ($CDCl_3$) 1.1–2.8 (m, 18 containing s, ca. 3 at 1.98), 4.53 ppm (br s, 2); *m/e* 224 (parent).

Catalytic Hydrogenation of 19. Formation of 21. A solution of 70 mg of **19** in 2 ml of ethanol was stirred over 10 mg of 10% palladium in charcoal under 1 atm of hydrogen. Filtration and evaporation of the volatiles at the water pump left a residue of 67 mg (96%) of **21** identical in all respects with a sample obtained from the experiments described above.

Preparation of *dl*-4aα-Acetoxymethyl-8aα-4,8β-dimethoxy-1,2,4a,5,8,8a-hexahydronapthalene-1,2-dione (28). To a solution of 2.00 g (9.50 mmol) of *o*-quinone **7** in 65 ml of absolute methanol was added 1.60 g (19.0 mmol) of 1-methoxy-1,3-butadiene. The orange solution was heated under reflux for 2 h under N_2. During this time the color turned light yellow. The mixture was cooled and evaporated to an oil to which 5 ml of benzene was added. The benzene solution was cooled in an ice bath and hexane was slowly added until crystallization appeared to be complete. The crystalline solid was filtered and washed with small amounts of ice-cold ether to afford 2.27 g (81%) of adduct **28** as a tan, crystalline solid: mp 157–158 °C; λ_{max} ($CHCl_3$) 6.25 μ; δ ($CDCl_3$) see structure **28** in text.

Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.22; H, 6.16. Found: C, 61.34; H, 5.99.

Reduction of 28. Formation of Tetrahydro Product 29. To a solution of 1.00 g (3.40 mmol) of **28** in 5 ml of dry tetrahydrofuran and 5 ml of absolute ethanol at 0 °C was added, with stirring, 257 mg (6.59 mmol) of $NaBH_4$. The solution slowly became homogeneous and was stirred under N_2 at 0 °C for 15 min. Stirring was continued at room temperature for an additional 4 h. The solution was poured into 15 ml of saturated KCl and 3 ml of water. The aqueous solution was extracted with 4 × 50 ml of ethyl acetate. The combined ethyl acetate extracts were dried over anhydrous Na_2SO_4 and evaporated in vacuo to afford 1.01 g (100%) of **29** as a yellow oil which became a crystalline mass: mp 75–80 °C; λ_{max} ($CHCl_3$) 2.85, 5.84, 6.08 μ; *m/e* 298 (parent).

Formation of *dl*-4aα-8aα-Acetoxymethyl-4ϵ-hydroxy-5β-methoxy-4a,5,8,8a-tetrahydronaphthalen-1(4*H*)-one (30). To a vigorously stirred solution of 1.10 g (3.7 mmol) of **29** in 3.5 ml of methylene chloride was added 10 ml of 10% (w/v) H_2SO_4. After 1 h, the phases were separated and the aqueous layer was extracted with 4 × 20 ml of methylene chloride. The combined methylene chloride extracts were dried over anhydrous Na_2SO_4 and evaporated to yield 955 mg (87%) of **30** as a clear oil: λ_{max} ($CHCl_3$) 2.85, 5.75, 5.95 μ; *m/e* 266 (parent).

Formation of 4aα-8aα-Acetoxymethyl-4ϵ-acetoxy-5β-methoxy-4a,5,8,8a-tetrahydronaphthalen-1(4*H*)-one (31). A solution of 0.950 g (3.60 mmol) of enone alcohol **30**, 3.0 ml of acetic anhydride, and 3.0 ml of pyridine was stirred at ambience for 12 h. The volatiles were removed in vacuo. The residual yellow oil was chromatographed on 20 g of silica gel. Elution with 3:2 benzene–ethyl acetate afforded 880 mg (80%) of crystalline enone diacetate: mp 81–82 °C (R_f 0.48, 3:2 benzene–ethyl acetate); λ_{max} ($CDCl_3$) 5.76, 5.94 μ; δ ($CDCl_3$) 1.83 (d, J = 21 Hz, 1), 2.01 (s, 3), 2.04 (s, 3), 2.62 (d, J = 21 Hz, 1), 2.99 (t, J = 7 Hz), 3.37 (s, 3), 3.92 (m, 1), 4.15 (d, J = 12 Hz), 4.50 (d, J = 12 Hz), 5.78 (m, 3), 6.10 (d, J = 11 Hz, 1), 6.86 ppm (d, d, J = 11, 5 Hz, 1).

Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54. Found: C, 62.35; H, 6.39.

Formation of *dl*-4aα-8aα-Acetoxymethyl-5β-methoxy-4a,5,8,8a-tetrahydronaphthalen-1(2*H*)-one (32). To a solution of 500 mg (1.60 mmol) of enone diacetate **31** in 16 ml of acetone under CO_2 was added 60 ml of 0.86 M $CrCl_2$[20] in water. The solution was stirred under CO_2 for 1 h, then extracted with 5 × 60 ml of ether. The combined ether extracts were dried over anhydrous Na_2SO_4 and evaporated in vacuo to yield 406 mg (100%) of β,γ-unsaturated ketone **32** [λ_{max} (neat) 5.76, 584 μ] as a yellow oil used directly in the next step.

Formation of *dl*-4aα-8aα-Acetoxymethyl-5β-methoxy-4a,5,8,8a-tetrahydronaphthalen-1(4*H*)-one (33). A solution of compound **32** (405 mg, 1.6 mmol) of β,γ isomer in 1.8 ml of tetrahydrofuran containing 0.03 ml of concentrated HCl was stirred at room temperature for 48 h. The volatiles were removed in vacuo. The yellow oily residue was dissolved in 2 ml of acetic anhydride and 2 ml of pyridine. The solution was stirred for 12 h at room temperature. The residue, obtained upon evaporation of the volatiles in vacuo, was chromatographed on 12 g of silicic acid. Elution with 3:2 benzene–ethyl acetate afforded 340 mg (84%) of **33** as a colorless oil which crystallized (mp 85–86 °C) on standing: λ_{max} ($CHCl_3$) 5.77, 598 μ; δ ($CDCl_3$) 1.8–3.0 (m, 8 containing s, ca. 3 at 2.0), 3.4 (s, 3), 3.9 (m, 1), 4.2 (d, J = 11 Hz, 1), 4.5 (d, J = 11 Hz, 1), 5.8 (br s, 2), 6.0 (d, t, J_d = 11, J_t = 2 Hz, 1), 6.8–7.3 ppm (m, 1).

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.27; H, 7.24.

Epoxidation of the Conjugated Double Bond of 34. Formation of *dl*-4aα-Acetoxymethyl-8aα-3,4ϵ-oxido-8β-methoxy-3,4,4a,5,8,8a-hexahydronaphalen-2(1*H*)-one (35). A solution of enone **34**[14b] (140 mg, 0.56 mmol) in 0.7 ml of methanol, 25 ml of 30% aqueous hydrogen peroxide, and 60 μl of 6 N aqueous sodium hydroxide was stirred for 2 h under nitrogen at room temperature. Dilution with 3 ml of water was followed by extraction with 5 × 10 ml of ethyl acetate. The combined ethyl acetate extracts were dried over anhydrous sodium sulfate. A residue of 97 mg, left upon evaporation of the volatiles in vacuo, was dissolved in 1 ml of acetic anhydride and 1 ml of pyridine. The solution was stirred for 12 h at room temperature. The volatiles were evaporated in vacuo and the residue was submitted to preparative TLC using 9:1 chloroform–acetone for elution. A fraction of 58 mg (39%) of epoxy ketone **35** was obtained as a clear, viscous oil: λ_{max} ($CHCl_3$) 5.75, 5.82 μ; δ ($CDCl_3$) 2.1 (s, 3), 3.3 (s, 3), 4.1 (d, J = 11.5 Hz, 1), 4.3 (d, J = 11.5 Hz, 1), 5.7 (br s, 2).

Formation of *dl*-4aα-8aα-Acetoxymethyl-1ϵ-hydroxy-5β-methoxy-1,4,4a,5,8,8a-hexahydronaphthalene (36). To a solution of 40 mg (0.15 mmol) of enone **35** in 0.5 ml of absolute methanol was added 24 mg (3 equiv) of hydrazine hydrate in 0.5 ml of absolute methanol immediately followed by 20 μl of glacial acetic acid. The reaction became exothermic and the mixture turned yellow as gas was evolved. After 1 h of stirring under N_2 at ambience, the reaction mixture had turned somewhat lighter in color. Water (2.0 ml) was added and this was extracted with 3 × 10 ml of ethyl acetate. The combined ethyl acetate extracts were dried over anhydrous Na_2SO_4 and evaporated in vacuo to afford an oil which was chromatographed on 4 g of silicic acid. Elution with 9:1 chloroform–acetone as an eluent gave 20 mg (53%) of the allylic alcohol **3** as an oil: λ_{max} ($CHCl_3$) 2.81, 5.76 μ; δ ($CDCl_3$) 1.4–2.7 (complex, 5), 2.1 (s, 3), 3.4 (s, 3), 3.4–4.2 (m, 3), 4.3 (s, 2), 5.6 (s, 2), 5.9 ppm (s, 2).

Oxidation of 36. Formation of 33. To a suspension of 23 mg (0.11 mmol, 1.52 equiv) of pyridinium chlorochromate[18] in 1.0 ml of methylene chloride was added a solution of 18 mg (0.071 mmol) of allylic alcohol **36** in 1 ml of methylene chloride. After 3 h, the solution was rapidly filtered through a plug of 1 g of Florisil using 100 ml of methylene chloride as an eluent. The collected methylene chloride was evaporated in vacuo to an oil which easily crystallized to afford 13 mg (73%) of enone **33**, mp 85–86 °C (mixture melting point, no depression) whose infrared and NMR spectra were identical with those of compound **33** prepared via the *o*-quinone route.

Preparation of 2-Methoxymethyl-4-aminoanisole (38). To a vigorously stirred suspension of 2-methoxymethyl-4-nitroanisole (**37**, 6.54 g, 0.033 mol) in 327 ml of 5% aqueous HCl was added 12 g of zinc dust. Stirring was continued for 30 min whereupon 15 ml of concentrated HCl and 10 g of zinc dust were added. Vigorous stirring was continued for an additional 30 min. The aqueous solution was filtered. After basification with solid potassium carbonate, the system was extracted with 4 × 150 ml of chloroform. The combined chloroform extracts were dried over anhydrous sodium sulfate. Evaporation of the volatiles afforded 4.92 g (89%) of **38** as a dark oil: λ_{max} ($CHCl_3$) 2.95, 3.01, 6.17 μ; δ ($CDCl_3$) 3.4 (s, 3), 3.5 (s, 2), 3.8 (s, 3), 4.5 (s, 2), 6.5–6.9 ppm (m, 3).

Preparation of 3-Methoxymethyl-4-methoxyphenol (39). To 2.0 l. of 0.1 M H_2SO_4 was added 11.44 g (68.5 mmol) of **38**. The solution was cooled to 0 °C and a solution of 5.06 g of $NaNO_2$ in 200 ml of water was added with stirring. After 10 min, 3.40 l. of 1.5 M $Cu(NO_3)_2 \cdot 6H_2O$ was added immediately followed by 12.00 g of Cu_2O. The solution was heated to 50 °C with stirring and maintained at that temperature for 30 min. A gas was evolved during this time and the solution became green. The aqueous system was extracted with 6 × 1 l. of chloroform. The combined chloroform extracts were dried over anhydrous $MgSO_4$ and evaporated to yield a black solid residue. The solid was dissolved in 1:1 ether–hexane with heat (steam bath) and allowed to crystallize slowly to afford 7.84 g (69%) of phenol **39**: mp 79–80 °C; λ_{max} ($CHCl_3$) 2.70, 2.94, 3.27 μ; δ ($CDCl_3$) 3.4 (s, 3), 3.8 (s, 3), 4.5 (s, 2), 3.5 (br s, 1), 6.6–7.0 ppm (m, 3).

Formation of 4-Methoxy-5-methoxymethyl-1,2-benzoquinone (40). To a solution of 1.40 ml of 1/6 M KH_2PO_4 in 1.40 l. of water at 0 °C was added 28 g of Fremy's salt.[12] A solution of 4.74 g (28.2 mmol) of phenol **39** in 15 ml of chloroform was added with vigorous stirring. After 30 min, the orange solution was extracted wih 6 × 200 ml of chloroform. The combined chloroform extracts were dried over anhydrous Na_2SO_4 and evaporated in vacuo to afford a dark red solid, which upon washing with 4 × 20 ml of ether and filtration gave 5.12 g (100%) of the *o*-quinone **40** as a bright red solid: mp 134.5–136 °C; λ_{max} ($CHCl_3$) 5.98 (br), 6.23 μ; δ ($CDCl_3$) 3.5 (s, 3), 3.9 (s, 3), 4.3 (d, J = 2.2 Hz, 2), 5.8 (s, 1), 6.5 ppm (t, J = 2.2 Hz, 1).

Anal. Calcd for $C_9H_{10}O_4$: *m/e* 182.05791. Found: *m/e* 182.05794.

Preparation of *dl*-4aα-Methoxymethyl-8aα-4,8β-dimethoxy-1,2,4a,5,8,8a-hexahydronaphthalene-1,2-dione (41). To a suspension of 5.00 g (27.5 mmol) of **40** in 200 ml of absolute methanol was added 6.00 g (71.4 mmol) of 1-methoxy-1,3-butadiene. The reaction mixture became homogeneous upon refluxing and slowly turned from red to yellow in color over a period of 9 h. Another 3 g (35.7 mmol) of 1-methoxy-1,3-butadiene was added and reflux was continued for an additional 3 h. Evaporation of the volatiles in vacuo gave a semicrystalline solid which was washed with 100 ml of ether to give 5.52 g (76%) of **41** as a white solid: mp 157.5–158.5 °C; λ_{max} ($CHCl_3$) 5.75, 5.99, 6.25 μ; δ ($CDCl_3$) 1.5–3.2 (complex, 3), 3.1–3.3 (m, 7 containing a singlet, ca. 2 at 3.2), 3.4 (d, J = 9 Hz, 1), 3.8 (s, 3), 4.0 (m, 1), 5.9 ppm (m, 3).

Reduction of 41 with Sodium Borohydride. Formation of Tetrahydro Product 42. To a suspension of 266 mg (1 mmol) of adduct **41** in 4 ml of absolute ethanol at 0 °C was added 65 mg (1.67 mmol) of $NaBH_4$. After stirring under N_2 at 0 °C for 15 min the solution was homogeneous. The solution was stirred at ambient temperature under N_2 for 4 h. The reaction mixture was poured into 25 ml of saturated KCl and 10 ml of water and extracted with 4 × 50 ml of ethyl acetate. The combined ethyl acetate extracts were dried over anhydrous Na_2SO_4 and evaporated in vacuo to afford 270 mg (100%) of an oil which crystallized on standing to give **42**: mp 145–145.5 °C; λ_{max} ($CHCl_3$) 2.76, 6.04 μ; *m/e* 270 (parent).

Anal. Calcd for $C_{14}H_{22}O_5$: *m/e* 270.146725. Found: *m/e* 270.146342.

Formation of *dl*-4aα-8aα-Methoxymethyl-4ϵ-hydroxy-5β-methoxy-4a,5,8,8a-tetrahydronaphthalen-1(4*H*)-one (43). To a solution of 270 mg (1 mmol) of diol **42** in 5 ml of methylene chloride was added 15 ml of 10% H_2SO_4 (w/v) with vigorous stirring. The two-phase system was stirred vigorously under N_2 for 40 min at room temperature. The layers were separated and the aqueous phase was

extracted with 4 × 50 ml of methylene chloride. The combined methylene chloride extracts were dried over anhydrous Na_2SO_4 and evaporated in vacuo to give 235 mg (99%) of 43 as an oil which could be crystallized by cooling: mp 54–55 °C; λ_{max} ($CHCl_3$) 2.71, 5.94 μ; δ ($CDCl_3$) 1.6–3.4 (complex, m, 11 containing 2 ca. 3 H singlets at 3.30 and 3.50), 3.8 (d, J = 10 Hz, 1), 4.2 (m, 1), 4.6 (br s, 1), 5.9 (s, 2), 6.1 (d, J_{AB} = 11 Hz, 1), 6.9 ppm (d, d, J_{BA} = 11, , J_{BX} = 5 Hz, 1).

Acetylation of 43. Formation of *dl*-4aα-8aα-Methoxymethyl-4ϵ-acetoxy-5β-methoxy-4a,5,8,8a-tetrahydronaphthalen-1-(4*H*)-one (44). A solution of 235 mg of **43** in 12 ml of acetic anhydride on 5 ml of pyridine was stirred at room temperature under nitrogen for 20 h. The volatiles were removed by pumping in vacuo to afford 273 mg (99%) of enone acetate **44** as an oil which slowly crystallized in the cold: mp 67.5–68 °C; λ_{max} ($CHCl_3$) 5.79, 5.96 μ; δ ($CDCl_3$) 1.5–3.4 (complex, m, 13 containing 3, ca. 3 H singlets at 2.0, 3.3, and 3.4), 3.7–4.1 (m, 2), 5.8 (m, 3), 6.1 (d, J_{AB} = 10.5 Hz, 1), 6.8 ppm (d, d, J_{BA} = 10.5 J_{BX} = 4.5 Hz, 1).

Anal. Calcd for $C_{15}H_{20}O_5$: *m/e* 280.13107. Found: *m/e* 280.13100.

Conversion of 44 to *dl*-4aα-8aα-Methoxymethyl-5β-methoxy-4a,5,8,8a-tetrahydronaphthalen-1(2*H*)-one (45). To a solution of 0.525 g (1.88 mmol) of acetoxy enone **44** in 40 ml of acetone under CO_2 was added with stirring 90 ml of 0.86 M chromous chloride[20] solution. The mixture was stirred under CO_2 for 45 min whereupon it was extracted with 3 × 100 ml of ether. The combined ether extracts were dried over anhydrous Na_2SO_4 and evaporated in vacuo to afford an oil which was chromatographed on 60 g of silica gel. Elution with 15% ethyl acetate in hexane gave 309 mg (75%) of **45** as an oil (R_f 0.67, 3:2 benzene–ethyl acetate): λ_{max} ($CHCl_3$) 5.77 μ; δ ($CDCl_3$) 1.1–2.6 (m, 3), 3.0 (m, 2), 3.1–1.40 (complex, 3), 3.35 (s, 3), 3.37 (s, 3), 5.4–6.1 ppm (m, 4).

Isomerization of 45. Formation of *dl*-4aα-8aα-Methoxymethyl-5β-methoxy-4a,5,8,8a-tetrahydronaphthalen-1(4*H*)-one (46). To a solution of 123 mg (0.55 mmol) of **45** in 2.5 ml of tetrahydrofuran was added 0.1 ml of concentrated HCl. The reaction mixture was stirred at room temperature under N_2 for 44 h. Analysis by TLC showed the reaction to be complete at this time. The volatiles were removed in vacuo and the residual yellow oil chromatographed on 10 g of silica gel. Elution with 5% ethyl acetate in hexane aafforded 115 mg (94%) of **46** as a crystalline solid: mp 52–53 °C; λ_{max} ($CHCl_3$) 6.00 μ; δ ($CDCl_3$) 1.3–2.6 (complex, 5), 3.0–3.5 (complex, m, 7, containing 2, ca. 3 H singlets at 3.3 and 3.4), 3.9–4.3 (m, 2), 5.8 (s, 2), 6.0 (d, t, J_d = 10, J_t = 2 Hz, 1), 7.0 ppm (d, t, J_d = 10, J_t = 4 Hz, 1); *m/e* 222 (parent).

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Registry No.—**7,** 54509-50-1; **13,** 59907-42-5; **15,** 59907-43-6; **16,** 59907-44-7; **17,** 59907-45-8; **18,** 59907-46-9; **19,** 59907-47-0; **20,** 59907-48-1; **21,** 59907-49-2; **22,** 59907-50-5; **23,** 59907-51-6; **24,** 59907-52-7; **25,** 59907-53-8; **28,** 59907-54-9; **29,** 59907-55-0; **30,** 59907-56-1; **31,** 59907-57-2; **32,** 59907-58-3; **33,** 59907-59-4; **34,** 59907-60-7; **35,** 59907-61-8; **36,** 59907-62-9; **37,** 59907-63-0; **38,** 59907-64-1; **39,** 59907-65-2; **40,** 59907-66-3; **41,** 559907-67-4; **42,** 59907-68-5; **43,** 59907-69-6; **44,** 59907-70-9; **45,** 59907-71-0; **46,** 59907-72-1; 1,3-butadiene, 106-99-0; 1-methoxy-1,3-butadiene, 3036-66-6.

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Reactions of Nitro Sugars. 37.[1] Preparation of Nitro Olefins via Methanesulfonates

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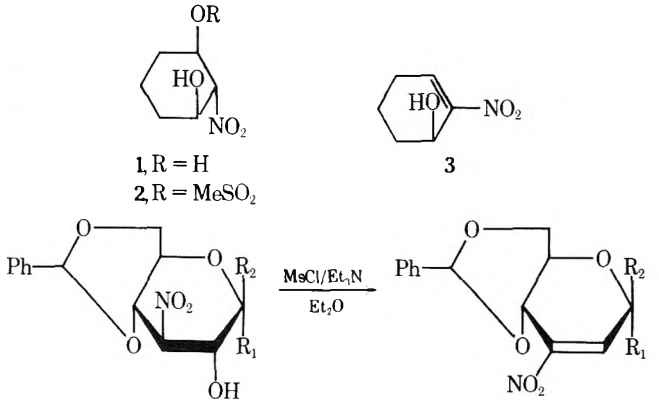
In continuation of our studies on the reactivity of nitro carbohydrates[1] we became interested in the preparation and the chemical behavior of *O*-methylsulfonyl derivatives. Such esters have not yet been described in the field of nitro sugars, and we were unable to find pertinent references in reviews[2-4] covering aliphatic nitro alcohols in general. Obviously, one should expect such mesylates to be useful intermediates for a variety of synthetic interconversions. The recent appearance of a brief note[5] reporting the dehydration of several simple nitro alcohols by the action of methanesulfonyl chloride and triethylamine (without isolation of intermediary mesylates) prompts us to disclose some results of our own work on this subject.

2-Nitro-1,3-cyclohexanediol (**1**), which served as a model compound, reacted with 1 molar equiv of mesyl chloride in dichloromethane, in the presence of triethylamine, to give its crystalline monomesylate (**2**) in approximately 60% yield. In addition, there seemed to arise some dimesylate (faster moving on TLC) and a small amount of olefin (**3**). Treatment of **2** with sodium bicarbonate in refluxing benzene for 3 h gave 2-nitrocyclohex-2-en-1-ol (**3**) which was readily isolated in 97% yield in this way whereas it had previously been obtained[6] by alkaline dehydration of **1** in lesser yield and only after column chromatographic purification.

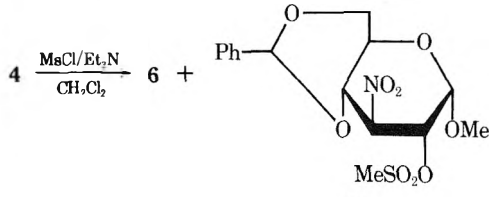


1, R = H
2, R = $MeSO_2$

3

4, R_1 = OMe; R_2 = H
5, R_1 = H; R_2 = OMe

6, R_1 = OMe; R_2 = H
7, R_1 = H; R_2 = OMe

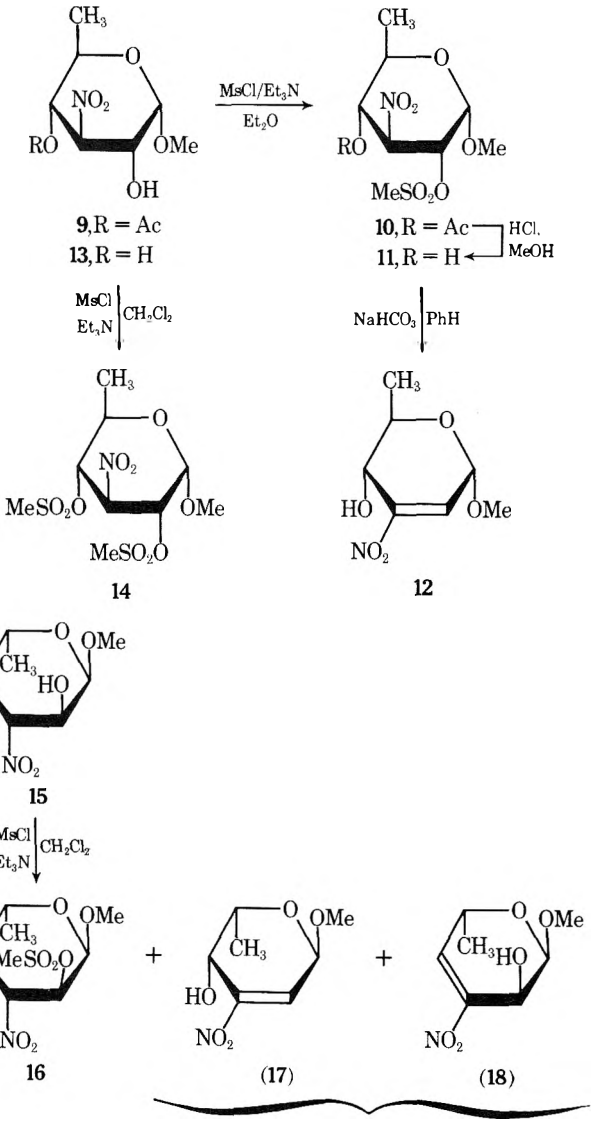


8

Methyl 4,6-*O*-benzylidene-3-deoxy-3-nitro-α-D-glucopyranoside (**4**) and its β anomer (**5**) were converted by mesyl chloride and triethylamine in ether (30 min at 25 °C) into the 2,3-unsaturated derivatives **6** and **7**, respectively, in yields of 80–90%. Although preparation of these nitro olefins from the alcohols by acetylation followed by dehydroacetoxylation can be done routinely,[7-9] the present procedure offers the advantage of greater simplicity and a much shorter reaction time.

In the case of the reaction of **4** we have been able to isolate intermediate 2-mesylate (**8**) in 20% yield when the reaction was carried out in dichloromethane, even though elimination giving **6** was predominant then too.

By contrast, mesylation of methyl 4-*O*-acetyl-3,6-dideoxy-3-nitro-α-D-glucopyranoside (**9**) gave in 80% yield the crystalline 2-mesylate (**10**). This product was first de-O-acetylated by acid-catalyzed methanolysis giving almost quantitatively methyl 3,6-dideoxy-2-*O*-methylsulfonyl-3-nitro-α-D-glucopyranoside (**11**), which was then converted into the olefin, methyl 2,3,6-trideoxy-3-nitro-α-D-*erythro*-hex-2-enopyranoside (**12**), by means of sodium bicarbonate in refluxing benzene (3 h; yield 92%). Elimination of methanesulfonic acid could also be effected with triethylamine but this required a longer reaction time and was accompanied by browning of the reaction solution.



9, R = Ac
13, R = H

10, R = Ac
11, R = H

14

12

15

16

(17)

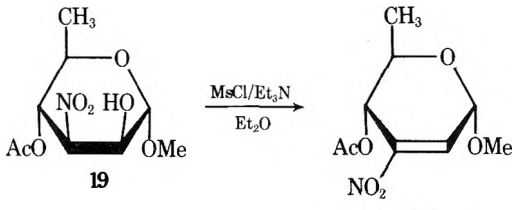
(18)

possible products; not separated and proved

Mesylation of **13** (the parent glycoside of **9** lacking the 4-*O*-acetyl group) likewise proceeded without a significant de-

gree of elimination; it gave the crystalline 2,4-dimesylate **14** in 75% yield. However **14**, similar to the monomesylate **11**, did suffer elimination on treatment with sodium bicarbonate in benzene at reflux for 12 h. Although investigation of this reaction has not yet been completed,[10] it is evident and noteworthy that the mesyl esters **10**, **11**, and **14** related to the 3,6-dideoxy-3-nitro-D-glucoside **13** are more stable than those derived from the 4,6-O-benzylidenated 3-deoxy-3-nitro-D-glucosides **4** and **5**. It was therefore interesting to study the behavior of stereoisomeric 3,6-dideoxy glycosides from the galacto and manno series.

Methyl 3,6-dideoxy-3-nitro-α-L-galactopyranoside (**15**) was mesylated by use of excess reagent. The reaction was relatively sluggish and no dimesylation was observed, but the 2-mesylate **16** was obtained crystalline in 48% yield. The remainder of the product was a syrupy mixture of what appeared to be mainly two compounds that failed to separate in column chromatography. The NMR spectrum of the mixture revealed that it contained nonmesylated nitro olefins, showing signals in the olefinic proton region (δ 7.0–7.3) but not in the mesyl group region (δ 3.0); OCH_3 and $C\text{-}CH_3$ signals occurred in their proper places. Evidently the galactoside **15**, unlike the glucoside **13**, underwent dehydration[11] to a considerable extent during the process of mesylation, which might suggest a lesser stability of its sulfonic esters. We were therefore surprised to find that the isolated monomesylate **16** was quite resistant to elimination as it remained unchanged for 6 h in refluxing benzene or toluene in the presence of sodium bicarbonate. One is thus led to conclude that **16** was not an intermediate in the formation of the olefins. Although the structures of the latter have not been established, formulas **17** and **18** suggest themselves at first glance and if they are correct it may be assumed that elimination involving the axial functionality at C-4 proceeds quite readily to give **18**, and that **17** owes its origin to allylic rearrangement of **18** which could possibly have occurred during the chromatographic processing. This idea is supported by the behavior of methyl 4-*O*-acetyl-3,6-dideoxy-3-nitro-α-D-mannopyranoside (**19**) in mesylation. In strong contrast to its α-D-gluco isomer (**9**), the mannoside **19** (whose free hydroxyl group is axial) was smoothly converted into the nitro olefin **20** (yield 65%) and no intermediary mesylate could be isolated.



19 **20**

In summary, we have shown that treatment of nitro sugars with mesyl chloride and triethylamine offers an attractive route to nitro olefinic derivatives which is potentially superior to the customary acetylation–dehydroacetoxylation sequence. However, the efficacy of the method varies and appears to depend on structural and configurational features in the substrate which influence the ease of formation and stability of intermediary methanesulfonate esters.

Experimental Section

Thin layer chromatography was performed on silica gel G (E. Merck) using, unless otherwise specified, 1:2 ethyl acetate–petroleum ether (solvent A) or 5% methanol in chloroform (solvent B) as the developing phase. All column chromatographic separations were routinely monitored by TLC. The NMR data refer to 100-MHz spectra of solutions in $CDCl_3$, internally standardized with tetramethylsilane. Infrared spectra were taken from Nujol mulls unless otherwise indicated. Optical rotations were recorded at room temperature in a Perkin-Elmer 141 automatic polarimeter.

***t*-2-Nitrocyclohexane-*r*-1,*c*-3-diol Monomethanesulfonate (2).** The diol[6,12] **1** (500 mg) was dissolved in dichloromethane (7 ml), and methanesulfonyl chloride (MsCl, 0.25 ml) was added with stirring at room temperature. After 5 min triethylamine (0.5 ml) was added under cooling of the reaction vessel with cold water. After 30 min, some remnant **1** and a strong, slightly faster moving spot due to **2** were seen by TLC with ethyl acetate–carbon tetrachloride (1:1). There were two additional, faint, fast-moving spots that were not identified. Anhydrous ether (10 ml) was added, an insoluble precipitate was removed, and the clear filtrate was evaporated with addition of several portions of 1-propanol. The resulting syrup was chromatographed on a column of silica gel (10 g) by means of the above TLC eluent. The fractions containing fast-moving by-products were discarded. Subsequent fractions that contained **2** only yielded a syrup from which two portions of added propanol were evaporated. The material then crystallized on standing overnight at 25 °C, yield 445 mg (60%) of crystalline **2**: mp 81–83 °C; ν_{max} (neat syrup) 3200–3600 (OH), 1550 (NO_2), and 1165 cm^{-1} (OMs); NMR δ 4.95 (1 H, sextet, J = 10 and 5 Hz, H-1), 4.47 (1 H, t, J = 10 Hz, H-2), 4.1 (1 H, m, sextet after D_2O exchange, H-3).

Anal. Calcd for $C_7H_{13}NO_6S$ (239.2): C, 35.14; H, 5.47; S, 13.40. Found: C, 35.19; H, 5.41; S, 13.18.

2-Nitrocyclohex-2-en-1-ol (3). A solution of **2** (300 mg) in dry benzene (3 ml) was heated for 3 h at reflux in the presence of dry sodium hydrogen carbonate (0.5 g). TLC with solvent A revealed total conversion of **2** into one faster migrating product. The cooled reaction mixture was filtered and the filtrate evaporated to give **3** as a colorless oil (175 mg, 97%). Its NMR spectrum ($CDCl_3$) agreed in every respect with that of **3** obtained previously by a different method.[6]

An attempt was made to prepare **3** directly from **1**, without the isolation of **2**, by carrying out the mesylation in *ether* solution (partial suspension) using double the amounts of mesyl chloride and triethylamine. Although **1** reacted completely according to TLC, the olefin **3** produced was accompanied by a product of very similar mobility (its mesyl derivative?), and **3** could only in part be separated by chromatography (yield 40%).

Methyl 4,6-*O*-Benzylidene-2,3-dideoxy-3-nitro-α-D-*erythro*-hex-2-enopyranoside (6). Nitro glycoside[13,14] **4** (100 mg) in andydrous ether (5 ml) was treated with methanesulfonyl chloride (0.05 ml) for 15 min at 20 °C, then triethylamine (0.06 ml) was added under cooling with water, and the mixture was stirred at room temperature for 45 min. At this time TLC (solvent A) indicated conversion of most of **4**, and the reaction was allowed to proceed for another 30 min. The supernatant solution was then decanted from a sticky, brown precipitate, washed with saturated, aqueous sodium bicarbonate solution followed by water, and dried over Na_2SO_4. Evaporation gave crystalline **6** (84 mg, 90%), mp 183–184 °C, undepressed upon admixture af authentic[7] **6**. The NMR spectrum was superimposable on that of authentic **6**.

Methyl 4,6-*O*-Benzylidene-3-deoxy-2-*O*-methylsulfonyl-3-nitro-α-D-glucopyranoside (8). To nitro glycoside **4** (200 mg) in dichloromethane (3 ml) was added MsCl (0.06 ml) and, after 5 min, triethylamine (0.08 ml) was added with stirring and external cooling by cold water. After 5 min, TLC (solvent A) showed a spot of **8** together with a stronger spot of faster moving **6**. Anhydrous ether (10 ml) was added to the reaction mixture which was stirred at 0 °C for 15 min; the precipitate was then removed by filtration and the filtrate evaporated to give a partially crystalline residue from which two portions of propanol were evaporated. The mixture was chromatographed on silica gel (7 g) with solvent A. This gave first **6** (123 mg, 65%), mp 183 °C, and secondly, **8** (50 mg, 20%): mp 215–216 °C; $[\alpha]_D$ +73.1° (c 0.6, chloroform); NMR δ 7.40 (5 H, Ph), 5.55 (1 H, s, PhCH), 5.1 region (3 H, unresolved, H-1, -2, -3), 4.37 (1 H, q, H-6, $J_{5,6}$ = 3, $J_{6,6'}$ = 9 Hz), 4.15 (m, 1 H, H-5), 3.7–4.0 (2 H, H-4 and -6′), 3.54 (3 H, s, OCH_3), 3.03 (3 H, s, OMs).

Anal. Calcd for $C_{15}H_{19}NO_9S$ (389.4): C, 46.26; H, 4.91; S, 8.23. Found: C, 46.10; H, 4.77; S, 8.15.

Methyl 4,6-*O*-Benzylidene-2,3-dideoxy-3-nitro-β-D-*erythro*-hex-2-enopyranoside (7). From the nitro glycoside[8,9,14] **5** (200 mg), the olefin **7** (74 mg, 78.5%) was obtained by exactly the same procedure as described above for **6**; the product was identified with an authentic sample[8,9] by an undepressed mixture melting point, 142–144 °C.

Methyl 4-*O*-Acetyl-3,6-dideoxy-2-*O*-methylsulfonyl-3-nitro-α-D-glucopyranoside (10). To a stirred solution of the 4-acetate[15] **9** (1.0 g) in anhydrous ether (15 ml) was added MsCl (0.5 ml) and, after 5 min, triethylamine (1.0 ml). The mixture was stirred for 10 min, after which **9** proved completely converted into **10** (TLC with solvent A). The solution was decanted from a sticky precipitate and evaporated to dryness with several additions of 1-propanol. The re-

maining syrup crystallized upon trituration with hexane. Recrystallized from ethyl acetate–petroleum ether, compound **10** (1.05 g, 80%) showed mp 161 °C; $[\alpha]_D$ +154° (*c* 1, chloroform), ν_{max} 1740 (OAc), 1560 (NO_2), and 1175 cm^{-1} (OMs); NMR δ 5 region (4 H, ring protons, unresolved), 3.88 (1 H, m, H-5), 3.50 (3 H, s, OCH_3), 3.01 (3 H, s, OMs), 2.10 (3 H, s, OAc), 1.24 (3 H, d, J = 6.5 Hz, C-CH_3).

Anal. Calcd for $C_{10}H_{17}NO_9S$ (327.3): C, 36.69; H, 5.23; S, 9.79. Found: C, 36.82; H, 5.25; S, 9.81.

Methyl 3,6-Dideoxy-2-*O*-methylsulfonyl-3-nitro-α-D-glucopyranoside (11). A solution of the 4-acetate **10** (900 mg) in acetone (1 ml) and 3% methanolic hydrogen chloride (9 ml of a solution that had been made by adding 1 ml of acetyl chloride to 20 ml of dry methanol) was kept at 40–50 °C for a few hours until TLC (solvent B) showed absence of starting material and sole presence of one new spot. The reaction mixture was then evaporated to give a brownish syrup which was passed through a 10-g silica gel column with ether to remove colored impurities. Evaporation of the effluent gave 772 mg of **11** which was recrystallized from ethyl acetate–petroleum ether to give pure **11** (768 mg, 98%): mp 106–107 °C; $[\alpha]_D$ +148° (c 1, chloroform); ν_{max} 3500 (OH), 1560 (NO_2), and 1170 cm^{-1} (OMs); NMR δ 3.49 (3 H, s, OMe), 3.03 (3 H, s, OMs), 1.36 (3 H, d, J = 6 Hz, C-Me).

Anal. Calcd for $C_8H_{15}NO_8S$ (285.3): C, 33.68; H, 5.30, S, 11.24. Found: C, 33.80; H, 5.30; S 11.39.

Methyl 2,3,6-Trideoxy-3-nitro-α-D-*erythro*-hex-2-enopyranoside (12). A solution of **11** (700 mg) in benzene (5 ml, dried over CaH_2) and dry sodium bicarbonate (2.5 g) were heated overnight at reflux. The mixture was allowed to cool, then filtered, and the filter residue was washed twice with chloroform. The combined filtrate was evaporated to give a brown syrup that was decolorized by passage through a 15-g silica gel column with ether. Evaporation of the effluent gave crude crystalline **12** which was recrystallized from chloroform–petroleum ether. The yield of pure **12** was 427 mg (92%), mp 124–125 °C (reported[17] for the L enantiomer, 124–125 °C). The NMR data of **12** were identical with those described[17] for its L enantiomer.

Methyl 3,6-Dideoxy-2,4-di-*O*-methylsulfonyl-3-nitro-α-D-glucopyranoside (14). The glucoside[15] **13** (200 mg) in dichloromethane (10 ml) was treated with MsCl (0.08 ml, 1 molar equiv) and triethylamine (0.14 ml) as described for previous experiments. After a reaction time of 5 min there was no change visible in TLC (solvent A). Therefore, five additional 0.08-ml portions of MsCl and equivalent amounts of triethylamine were added in 5-min intervals, without cooling. Eventually progress of reaction resulting in complete consumption of **13** was noted. Ether was then added to the reaction mixture to precipitate salt which was removed. On evaporation the filtrate gave a brownish residue which was repeatedly evaporated with 1-propanol until the smell of MsCl was no longer noticeable. The residue then crystallized copiously upon trituration with ice water. The material was washed with cold water, dissolved in ethyl acetate, dried with Na_2SO_4, and recrystallized by addition of petroleum ether. The yield was 260 mg (74%): mp 132–132.5 °C; $[\alpha]_D$ +110.5° (*c* 0.4, chloroform); ν_{max} 1555 (NO_2), 1170 cm^{-1} (OMs); NMR δ 4.7–5.1 (4 H, ill resolved, H-1, -2, -3, -4), 3.93 (octet, 1 H, H-5, $J_{4,5}$ = 10, $J_{5,6}$ = 6 Hz), 3.51 (s, 3 H, OMe), 3.01 and 3.03 (2 s, 6 H, 2 OMs), 1.44 (d, 3 H, J = 6 Hz, C-Me).

Anal. Calcd for $C_9H_{17}NO_{10}S_2$ (363.4): C, 29.74; H, 4.71; S, 17.64. Found: C, 29.73; H, 4.79; S, 17.66.

Methyl 3,6-Dideoxy-2-*O*-methylsulfonyl-3-nitro-α-L-galactopyranoside (16). The galactoside[16] **15** (300 mg) in dichloromethane (7 ml) was treated with MsCl (0.1 ml) and triethylamine (0.2 ml in 1 ml of dichloromethane). The mixture was stirred for 90 min at 25 °C, after which period TLC (solvent A) indicated reaction to be incomplete. When the TLC pattern remained unchanged after 4 h, a second and a third set of MsCl and TEA were added with a 30-min interval. This caused the reaction to become nearly complete, with only a trace of **15** remaining. Final addition of a fourth set of reagent portions resulted in complete disappearance of **15**. There was one major product spot (**16**) and a quite strong spot that migrated faster (and was seen, by application of another solvent, to be inhomogeneous). The reaction mixture was partially evaporated to a volume of 5 ml, ether (10 ml) was added, and the mixture was kept in a refrigerator for 2 h and then filtered. The filtrate was evaporated with several additions of 1-propanol, and the resulting syrup was chromatographed on silica gel (10 g) using chloroform as eluent. Fractions containing fast-moving material yielded a thick oil (135 mg) which was seen by TLC (with chloroform) to consist of two components moving close together. The NMR spectrum of the oil suggested the presence of two nonmesylated, unsaturated glycosides, one of which appeared to preponderate. There were signals (total intensity 1 H) in the δ 7.0–7.3 region (nitro olefinic protons), unresolved signals (4 H) at δ 3.6–5.3, two 3 H signals close together near δ 3.5 (OCH_3), and two overlapping 3 H doublets centered at δ 1.5 (C-CH_3). Further elution of the column gave syrupy **16** which crystallized on standing for a few hours: large plates (200 mg, 48%); mp 175–176 °C; $[\alpha]_D$ −206.6° (*c* 0.2, chloroform); ν_{max} 3570 (OH), 1555 (NO_2), 1160–1170 cm^{-1} (OMs); NMR δ 5.30 (1 H, q, $J_{1,2}$ = 3.7, $J_{2,3}$ = 11 Hz, H-2), 5.13 (1 H, d, H-1), 4.92 (1 H, q, $J_{3,4}$ = 3 Hz, H-3), 4.4 (1 H, m, H-4), 4.13 (1 H, q, H-5), 3.50 (3 H, s, OCH_3), 3.14 (3 H, s, OMs), 1.32 (3 H, d, J = 7 Hz, C-CH_3).

Anal. Calcd for $C_8H_{15}NO_8S$ (285.3): C, 33.68; H, 5.30; S, 11.24. Found: C, 33.54; H, 5.19; 11.12.

Attempted elimination of the mesyloxy group by refluxing **16** in the presence of sodium bicarbonate in benzene or toluene for 6 h was unsuccessful. The compound remained unchanged.

Methyl 4-*O*-Acetyl-2,3,6-trideoxy-3-nitro-α-D-*erythro*-hex-2-enopyranoside (20). The 4-acetate[15] **19** (100 mg) in anhydrous ether (5 ml) and MsCl (0.02 ml) were stirred for 15 min after which triethylamine (0.5 ml) was added with water cooling. Stirring was continued for 45 min at room temperature. Processing of the mixture as previously described furnished crude **20** as a yellowish syrup which after purification by passage through silica gel (5 g) gave crystalline **20** (60 mg, 65%), mp 81–82 °C (reported[17] for L enantiomer, 81–81.5 °C).

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Registry No.—**1**, 38150-01-5; **2**, 59790-62-4; **3**, 51254-77-4; **4**, 3650-60-0; **5**, 25541-57-5; **6**, 16697-51-1; **7**, 25541-58-6; **8**, 59734-05-3; **9**, 59790-63-5; **10**, 59790-64-6; **11**, 59790-65-7; **12**, 59790-66-8; **13**, 43138-55-2; **14**, 59790-67-9; **15**, 22224-31-3; **16**, 59790-68-0; **19**, 59790-69-1; **20**, 59790-70-4; methanesulfonyl chloride 124-63-0.

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Solid-State Conformations of Vitamin D_3

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Discoveries within the last 10 years of active metabolites and synthetic analogues of vitamins D_2 (ergocalciferol) and D_3 (cholecalciferol) have stimulated much research in this area

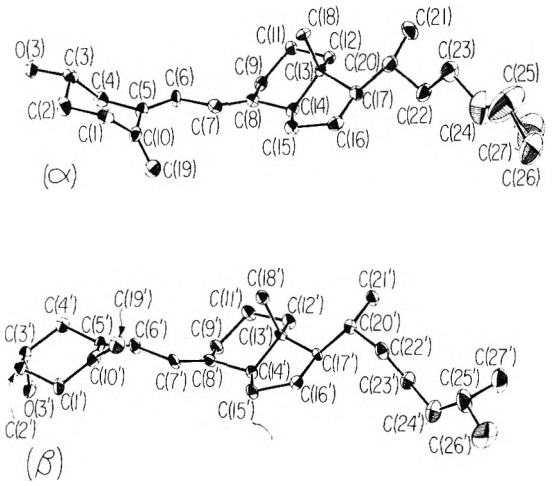

Figure 1. The α and β conformers of vitamin D_3. The thermal ellipsoids of the nonhydrogen atoms in Figures 1 and 3 are scaled at a 15% probability level.

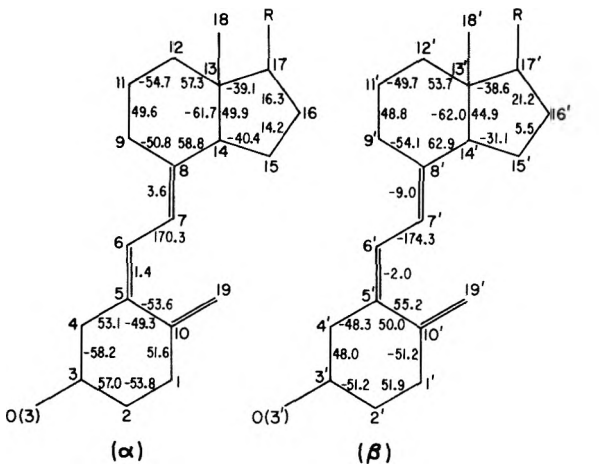

Figure 2. Torsional angles for the two vitamin D_3 conformers. The R substituent at C(17) and C(17′) denotes the $-CH(CH_3)-CH_2CH_2CH_2CH(CH_3)_2$ side chain.

which has produced important advances regarding their uses in both medicine and nutrition.[1] Investigations of the modes of vitamin D action at the molecular level necessitate a detailed knowledge of their molecular topologies. Results from several recent ^1H NMR investigations[2-4] on the solution conformations for vitamin D_2[2] and for vitamin D_3 and several metabolites including $1\alpha,25\text{-}(OH)_2\text{-}D_3$,[3,4] with computations based on the crystallographic parameters of two analogues of vitamin D_2, viz., its 4-iodo-5-nitrobenzoate ester (INC)[5] and the 3,20-bis(ethylenedioxy) derivative (ECF),[6] have all been consistent with Havinga's proposal[7] that in solution the ring A of a vitamin D molecule exists in a dynamic equilibrium between the α chair form (in which the CH_2 group is situated below the mean A ring plane) and the β chair form (in which the CH_2 group is situated above the mean A ring plane). As part of a systematic stereochemical investigation in an attempt to correlate the structures of various vitamin D molecules with their properties and biological activities, we report here the outcome of an x-ray diffraction analysis which shows that vitamin D_3 crystallizes in an equimolar ratio of the above two conformers with the 3-OH substituent occupying an equatorial position in the α form and an axial position in the β form.[8] Besides being in accord with the NMR solution conformational analyses, this study also furnishes molecular parameters for both unsubstituted vitamin D_3 conformers and thereby provides clear evidence that the adoption of ring A of a vitamin D molecule to either the α or β chair form does not markedly influence the apparently rigid conformation of the seco-B ring.

Figure 1 shows the two independent molecules of vitamin D_3 displaying different solid-state conformations of the A ring corresponding to those inferred in solution from the ^1H NMR analyses.[2-4] Although the cyclohexane-like A ring in both molecules has a chair conformation, it is apparent that in molecule α (which adopts the α form) the hydroxyl group at C(3) occupies the equatorial position and the $C(19)H_2$ group lies below the mean ring plane, whereas in molecule β (which adopts the β form) the hydroxyl group at C(3′) occupies the axial position and the $C(19')H_2$ group lies above the mean ring plane. Corresponding torsional angles (Figure 2) in the A and seco-B rings reflect these two different A ring conformations by having opposite signs in the two molecules. Although corresponding torsional angles in the C–D fused ring system in the two molecules have the same signs, a detailed analysis[9] shows that ring D possesses an essentially half-chair conformation in the α form and a C(13)-envelope conformation in the β form.

The observation that both the mean torsional angles of 53.8 and 50.1° in ring A of molecules α and β, respectively, are smaller than the corresponding experimental value of 55.9° found[10] in cyclohexane can readily be attributed to the flattening effect caused by the two exocyclic double bonds. A further examination of the corresponding torsional angles for both conformations of ring A indicates that the axial 3-OH substituent in the β form induces a significant flattening effect reflected in the two torsional angles C(1′)–C(2′)–C(3′)–C(4′) and C(2′)–C(3′)–C(4′)–C(5′) being only −51.2 and 48.0°, respectively, in contrast to the equatorial 3-OH substituent in the α form which allows much larger corresponding torsional angles (viz., 57.0 and −58.2°, respectively). The smaller values than 55.9° for these above two torsional angles in the β form and the larger values than 55.9° for the corresponding angles in the α form are deemed to be a consequence not only of intramolecular interactions per se but also, at least in part, to the influence of close-packing interactions of the A rings resulting from the stereochemical requirements of the strong hydrogen-bonding network on the 3-OH substituents (vide infra).[11]

The similarity between the absolute magnitudes of the torsional angle of −53.6° for the C(6)=C(5)–C(10)=C(19) fragment in the α form and the torsional angle of 55.2° for the corresponding fragment in the β form indicates that the result of the steric constraint of the A ring on the large twisting of the above exocyclic cis-diene system from planarity is practically the same in the α and β forms. Torsional angles for the C(5)=C(6)–C(7)=C(8) and C(5′)=C(6′)–C(7′)=C(8′) trans-diene system of 170.3 and −174.3°, respectively, show that the seco-B rings in these two conformers possess a nearly planar arrangement such that the trans-diene geometries (which are almost mirror images of each other in the α and β forms) are essentially unaltered upon a change in the A ring conformation. Figures 1 and 3 show that both conformers of vitamin D_3 (including the side chain) exist in an extended fashion with the longest intramolecular distance between nonhydrogen atoms being 17.4 Å for O(3)···C(26) in molecule α and 15.8 Å for C(3′)···C(26′) in molecule β.

Figure 3 is a view showing the particular hydrogen-bonding network of crystalline vitamin D_3 resulting from the interactions of the 3-hydroxyl substituents of the two types of conformers. The molecules are well separated in the unit cell with all intermolecular nonhydrogen contacts being greater than 3.4 Å except for the relatively short O–H···O distances of 2.71 (1) and 2.73 (1) Å, which indicate reasonably strong O–H···O bonds. It is concluded that the crystal packing of vitamin D_3 including the presence of both conformers is mainly dictated

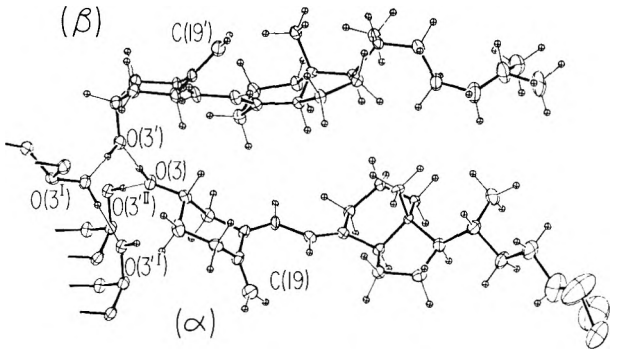

Figure 3. Hydrogen bonding scheme showing the α and β conformers connected in the crystalline state by their single hydroxyl groups to form an infinite spirallike hydrogen-bonded oxygen chain. Each helical chain is constrained about a 2_1 axis in the b direction, with the two conformers occupying alternating positions. $O(3^I)$ and $O(3'^I)$ are related to O(3) and O(3'), respectively, by the screw axis, while $O(3'^{II})$ is related to $O(3'^I)$ by a whole lattice translation along the b axis. The unusually large thermal ellipsoids for the isopropyl carbon atoms at the end of the side chain of the α conformer relative to those for the other nonhydrogen atoms are attributed at least in part to these atoms possessing more than one crystal orientation.

by the steric constraints imposed by the infinite helical hydrogen-bonded oxygen chain.

Experimental Section

Vitamin D_3, $C_{27}H_{44}O$, crystallizes with eight molecules in an orthorombic unit cell of dimensions a = 19.730 (4), b = 7.340 (2), and c = 35.716 (6) Å, and of symmetry $P2_12_12_1$ such that the two conformers comprise the crystallographically independent unit.

Intensity data were collected on a Datex-controlled, General Electric diffractometer with an E&A full circle to $2\theta \leq 120°$ with Cu Kα (1.5418 Å) radiation. The data processing included an intensity correction for crystal decay (i.e., ca. 20% over the entire data collection). Of the 4366 measured crystallographically independent reflections, the 2585 reflections for which $I \geq 2\sigma(I)$ were used in the structural analysis.

The structure was solved by the application of MULTAN.[12,13] An E map revealed 34 of the 56 independent nonhydrogen atoms. Subsequent Fourier syntheses yielded unambiguous locations for all nonhydrogen atoms except for the three end carbon atoms [viz., C(25), C(26), and C(27)] on the side chain in one of the two independent molecules. Fourier and difference Fourier maps consistently showed a cluster of small electron-density peaks which from stereochemical considerations was completely compatible with a crystal disorder for this isopropyl carbon fragment. The results reported here are based upon a refinement in which the three strongest peaks in the cluster were taken as whole-weighted occupancies for these carbon atoms. Idealized positions for the hydrogen atoms (except for those attached to the three crystal-disordered carbon atoms) were calculated and then included in the structure factor calculations as fixed-position atom contributors in the final anisotropic full-matrix least-squares refinement which yielded an unweighted $R_1(F)$ index of 8.7% and a weighted $R_2(F)$ index of 10.0%. Bond distances and angles are within their expected ranges[13] except for those corresponding to the three carbon atoms at the end of the side chain of one of the two independent molecules (due to a crystal disorder of this isopropyl carbon fragment).

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Supplementary Material Available. Tables of atomic parameters, bond distances, and bond angles along with their estimated standard deviations (11 pages). Ordering information is given on any current masthead page.

Registry No.—Vitamin D_3, 67-97-0.

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3-*O*-α-L-Rhamnopyranosyl-D-glucose, a New Disaccharide Synthesized by the Koenigs–Knorr Reaction

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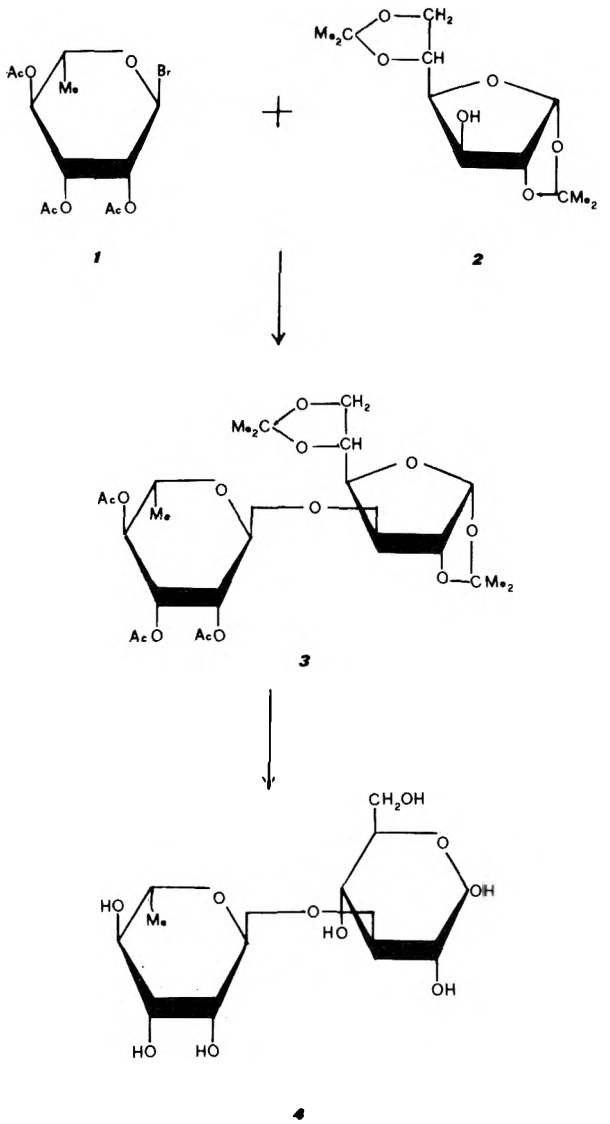
The Koenigs–Knorr reaction is probably the most widely applicable and important method for the condensation of two monosaccharide units; by using this reaction, 2-*O*-β-D-glucopyranosyl-D-xylose,[1] rutinose[2] (6-*O*-α-L-rhamnopyranosyl-D-glucose), robinobiose[3] (6-*O*-α-L-rhamnopyranosyl-D-galactose), and other disaccharides have been synthesized. The present work deals with the synthesis of 3-*O*-α-L-rhamnopyranosyl-D-glucose, a new disaccharide prepared by the Koenigs–Knorr reaction. This preparation was carried out as follows (Scheme I): α-acetobromorhamnose (1) was condensed with 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (2) in the presence of mercuric acetate to form the compound **3** which on deacetylation with sodium methoxide and hydrolysis with oxalic acid gave 3-*O*-α-L-rhamnopyranosyl-D-glucose (**4**) in a overall yield of 10%. The structure of this disaccharide was

Scheme I



determined as follows: acid hydrolysis (10% acetic acid, 3.5 h under reflux) gave rhamnose and glucose identified by paper chromatography; methylation of disaccharide with methyl iodide in dimethylformamide in the presence of silver oxide followed by acid hydrolysis (0.3 N HCl; 4 h under reflux) gave 2,3,4-tri-*O*-methyl-L-rhamnose and 2,4,6-tri-*O*-methyl-D-glucose identified by paper chromatography and thin layer chromatography. The configuration of the glycosidic linkage of this disaccharide was indicated by the similarity of the optical rotation ($[\alpha]_D$ +4) to that ($[\alpha]_D$ −0.1) of isomeric disaccharide rutinose for whose configuration independent evidence was obtained by Gorin and Perlin.[4]

The α-L-glycosidic linkage was confirmed by ^1H NMR spectroscopy (D_2O). Table I shows the chemical shifts of H-1 proton signals of the rhamnose moiety in some compounds. From the above data it appears that the configuration of the glycosidic linkage in the synthesized disaccharide is α since the chemical shifts of the H-1 proton signal of the rhamnose moiety would be expected at a higher value of τ for the β configuration.[5]

Table I. Chemical Shifts of H-1 Proton Signals of the Rhamnose Moiety in Some Compounds

Compd	Chemical shift, $\tau(D_2O)$
Rutinose	4.91
4-*O*-α-L-Rhamnopyranosyl-D-glucose	4.90
3-*O*-α-L-Rhamnopyranosyl-D-glucose	4.92
α-Methyl-L-rhamnopyranoside	4.88
β-Methyl-L-rhamnopyranoside	5.24

Experimental Section

^1H NMR spectra were taken at 100 MHz on a Varian HA-100 in D_2O (DSS as internal reference, τ 10). Rutinose was prepared from rutin by controlled acid hydrolysis; an authentic sample of 4-*O*-α-L-rhamnopyranosyl-D-glucose was supplied by Dr. G. O. Aspinall (York University, Ontario). α- and β-methyl-L-rhamnopyranoside were prepared according to Hough et al.[6]

3-*O*-α-L-Rhamnopyranosyl-D-glucose. A mixture of 0.68 g of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, mercuric acetate (0.25 g), and α-acetobromorhamnose (0.66 g) was shaken in dry benzene (10 ml) for 4 days protected from atmospheric moisture in the dark at room temperature. The reaction mixture was washed twice with water, dried (Na_2SO_4), and filtered; removal of the solvent gave 0.55 g of residue (A). The acetyl groups were removed by shaking a solution of A in methanol (4 ml) with 0.1 N sodium methoxide (0.5 ml) at room temperature for 6 h, followed by neutralization with aqueous oxalic acid. Removal of most of the methanol at 40 °C (15 mm) was followed by the removal of isopropylidene groups by treatment of the residue with oxalic acid (0.01 N, 10 ml) at 100 °C for 3 h. After neutralization with barium carbonate and filtration, the remaining ions were removed by Amberlite IR-100H and IR-4B ion-exchange resins. Evaporation of the water left a colorless syrup (B). Examination on a paper chromatogram (solvent mixture: 1-butanol–acetic acid–water, 12:3:5) showed the presence of rhamnose (R_G 2.04), glucose (R_G 1), and a substance with R_G value 0.92 (3-*O*-α-L-rhamnopyranosyl-D-glucose). The syrup (B) was dissolved in water and from this solution the disaccharide was isolated by preparative chromatography on Whatman 3MM paper (solvent mixture: 1-butanol–acetic acid–water, 12:3:5). The bands (R_G 0.92) located by a test strip with aniline phosphate were excised and extracted with water. The aqueous extracts on evaporation to dryness in vacuo gave 62 mg of 3-*O*-α-L-rhamnopyranosyl-D-glucose ($[\alpha]_D$ +4 in water).

Acid Hydrolysis of Disaccharide. A solution of disaccharide (50 mg) in 10% acetic acid (50 ml) was refluxed for 3.5 h. The hydrolysate was evaporated to dryness in vacuo and excess acetic acid was removed by adding a small amount of water to the residue and evaporating to dryness. Examination on a paper chromatogram (solvent mixture: 1-butanol–acetic acid–water, 12:3:5) showed the presence of rhamnose and glucose.

Methylation of Disaccharide. 3-*O*-α-L-Rhamnopyranosyl-D-glucose (50 mg) was dissolved in dimethylformamide (20 ml); methyl iodide (20 ml) and silver oxide (5 g) were added. The mixture was stirred at room temperature in the dark for 18 h and filtered. The solution was evaporated to dryness and the residue dissolved in 0.3 N HCl (50 ml) and refluxed for 4 h; after cooling, the solution was taken to dryness in vacuo. The residue, dissolved in water, was analyzed for methylated sugars by paper chromatography according to Petek[7] and thin layer chromatography on silica gel (solvent mixture: ethyl acetate–chloroform, 1:1). 2,3,4-Tri-*O*-methyl-L-rhamnose and 2,4,6-tri-*O*-methyl-D-glucose were identified.

Acknowledgment. The author thanks Professor M. Piattelli (Catania, Italy) for his interest in this work and Dr. G. O. Aspinall (York University, Ontario) for a sample of 4-*O*-α-L-rhamnopyranosyl-D-glucose from gum arabic.

Registry No.—**1**, 5158-64-5; **2**, 582-52-5; **4**, 36506-90-8; 2,3,4-tri-*O*-methyl-L-rhamnose, 7439-05-6; 2,4,6-tri-*O*-methyl-D-glucose, 4578-22-7.

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Marine Natural Products: Isodactylyne, a Halogenated Acetylenic Ether from the Sea Hare *Aplysia dactylomela*[1]

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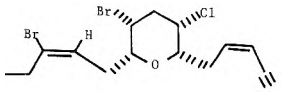
Received March 9, 1976

In a previous communication[2] we reported the structure of dactylyne (1), which was isolated from the sea hare *Aplysia dactylomela*. We report herein the isolation of an isomeric halogenated acetylenic ether, isodactylyne, from the same source and present evidence for assigning it the structure **2**.



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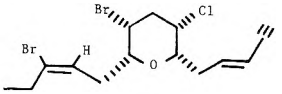

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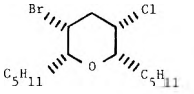
These two halogenated ethers are members of a group of similar nonterpenoid C-15 ethers elaborated by red algae.[3]

Isodactylyne, a colorless oil, $[\alpha]^{24}D$ −8.06°, was isolated by chromatography from the hexane extracts of whole, dried sea hares. Purified, neat samples of isodactylyne deteriorated slowly at room temperature and hence no combustion analysis was obtained. Mass spectral analysis established that this new halogenated ether has the same elemental composition ($C_{15}H_{19}OBr_2Cl$) as dactylyne; indeed, the fragmentation patterns of **1** and **2** were virtually identical. The presence in **2** of a terminal acetylene group conjugated with a double bond was indicated by ir (3300, 2095 cm^{-1}) and uv data (λ_{max} 224 nm, shoulder at 233 nm; ϵ_{max} 15 500). The larger extinction coefficient in the uv spectrum of **2** relative to that of **1**[1] suggested the trans geometry for the double bond of the enyne group.[4]

Comparison of the NMR spectra of isodactylyne and dactylyne, see Figure 1, revealed great similarity in structure between the two, and at the same time confirmed that the enyne double bond of **2** is trans, as evidenced by the large coupling constant of the olefinic protons of the enyne group, δ 5.65 (broadened d, J = 16, 1–2 Hz), 6.24 (doubled t, J = 16, 7 Hz).[5] The triplet multiplicity in the δ 6.24 signal indicated coupling of this olefinic proton with an adjacent methylene group, thus confirming that the enyne side chain consisted of at least five carbons.

The olefinic proton signal centered at δ 5.80 (t, J = 8 Hz) and the entire upfield portion of the spectrum of isodactylyne resembled that of dactylyne to such a degree that a direct correspondence in structure at many points could be inferred. In fact, catalytic hydrogenation of **2** afforded a solid octahydromonodebromo product, mp 51.0–52.2 °C, M^+ m/e 342, 340, 338 ($C_{15}H_{28}BrClO$), which was identical with that obtained



3

from dactylyne as judged by melting point, mixture melting point, R_f value, optical rotation, and ir, NMR, and mass spectra. This confirmed that **1** and **2** were identical with respect to carbon skeleton, size and location of the ether ring, type of halogen substitution on the ring, and relative stereochemistry of all ring substituents. In view of this confirmation of the C-5 length for both side chains in isodactylyne, the enyne chain could be formulated conclusively as shown in **2**.

The side chain bearing the vinyl bromide group is assigned

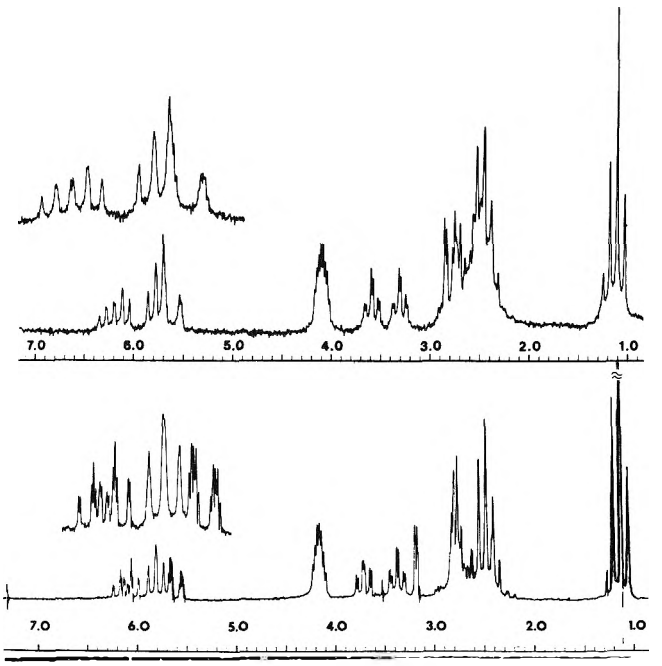


Figure 1. 100-MHz NMR spectra of dactylyne (1) (bottom) and isodactylyne (2) (top).

the same structure as the one in dactylyne on the basis of NMR data. The location of the bromine was established by showing that the signal due to the methylene unit of the ethyl group was a quartet (irradation at δ 1.13 collapsed the two intense lines centered at δ 2.50 to a singlet at that position). The vinyl bromide group is assigned the E configuration since the olefinic proton of this unit resonates at exactly the same position as does the corresponding proton in **1**, whereas a chemical shift difference would have been expected[6] if the configuration at this center were different for **1** and **2**.

Combination of the foregoing conclusions yields the structure **2** for isodactylyne, including the absolute stereochemistry implied thereby. An alternate structure for isodactylyne in which the location of the ring halogens is reversed and the configuration at all chiral centers is inverted would also give rise to the octahydromonodebromo derivative **3** upon hydrogenation. However, the configurtion shown for **2** is considered biogenetically more probable in the light of the established structure for dactylyne.

The assignment of the signals in the δ 3.2–4.2 region of the spectrum of isodactylyne parallels those for dactylyne.[2] Although we have isolated dactylyne and isodactylyne from a sea hare, these compounds undoubtedly come from the algae on which the mollusc feeds. Such a food chain source has been confirmed earlier for natural products isolated from *Aplysia californica*.[7]

Experimental Section[8]

Isolation of Dactylyne (1) and Isodactylyne (2). Specimens of *Aplysia dactylomela* collected in the environs of Bimini, Bahamas, were pierced and preserved whole in 2-propanol for shipment. Shortly after the specimens were received in our laboratories, sufficient water was added to bring the preservation solution to a 40/60 (v/v) water/alcohol mixture, and the specimens were allowed to soak for an additional 2 days. The bodies were then recovered by decantation and filtration, air dried (3.5 kg dry wt), broken into small pieces, and extracted in a Soxhlet apparatus with distilled hexane for 2–4 days. The hexane extract was filtered and the solvent evaporated to yield 204 g of a dark green oil.

A portion of this crude hexane extract (100 g) was chromatographed on Florisil (1500 g). One-liter fractions were collected employing the following elution scheme: hexane, fractions 1–7; benzene/hexane (1/3), fractions 8–11; benzene/hexane (1/1), fractions 12–18; benzene (2-l. fractions), fractions 19–22; ethyl acetate (one 8-l. fraction). Fractions

exhibiting similar TLC profiles were combined. A portion (2.5 g) of combined fractions 9–11 (16.45 g) was chromatographed on 40 g of thin layer mesh silica gel H using ether/hexane (5/95) as solvent and collecting 20-ml fractions. Dactylyne (175 mg) crystallized from the material obtained in fractions 18–20 (290 mg). Recrystallization from an ether/hexane mixture yielded large, colorless crystals roughly trapezoidal in shape which were utilized for x-ray crystallographic analysis.[2] After 29 fractions had been collected, one 250-ml fraction was collected and this yielded 170 mg of material, homogeneous by TLC. Chromatography of this fraction on thin-layer mesh silica gel gave 160 mg of isodactylyne (**2**). All attempts to crystallize isodactylyne were unsuccessful.

Isodactylyne had $[\alpha]^{24}D$ −8.06 ° (*c* 7.97, $CHCl_3$); R_f 0.46 (1:1 benzene/hexane, silica gel H); ir (neat) 3300, 3030, 2970, 2930, 2830, 2085 (weak), 1640, 1415, 1345, 1315, 1080 (br), 955, 870, 750, and 600 cm^{-1}; uv (isooctane) λ_{max} 224 nm (ϵ_{max} 15 500), with an inflection at 233 nm; 100-MHz NMR ($CDCl_3$), see Figure 1; mass spectrum (70 eV) *m/e* (rel intensity) M^+, 412 (3), 410 (4), 408 (2), 377 (1), 375 (2), 373 (1), 345 (2), 343 (3), 341 (2), 337 (7), 331 (16), 329 (10), 251 (3), 249 (5), 247 (1), 229 (3), 227 (4), 225 (1), 187 (5), 185 (10), 183 (10), 182 (8), 153 (15), 149 (24), 147 (28), 146 (15), 145 (14), 129 (11), 119 (29), 118 (18), 117 (51), 115 (14), 107 (11), 105 (20), 103 (31), 95 (11), 93 (10), 91 (34), 81 (23), 79 (30), 78 (18), 77 (19), 75 (10), 69 (13), 67 (65), 64 (100) base peak, 57 (15), 55 (18), 53 (27), 51 (12), 41 (40).

Pure dactylyne had mp 62.5–63.5 °C; $[\alpha]^{23}D$ −36.2° (*c* 15.2, $CHCl_3$); R_f 0.57 (1:1 benzene/hexane, silica gel H).

Octahydromonodebromodactylyne (3). A. From Dactylyne (1). To a stirred suspension of 30 ml of ethyl acetate containing a few milligrams of prereduced PtO_2 in a hydrogen atmosphere (1 atm) was added 105 mg of dactylyne dissolved in 10 ml of ethyl acetate. Hydrogenation was continued overnight, then the reaction mixture was filtered and the filtrate concentrated on a rotary evaporator to yield 77.8 mg (89.4%) of a clear, colorless oil which solidified after removal of the last traces of solvent under high vacuum. Recrystallization of the crude product from 95% ethanol yielded pure octahydromonodebromodactylyne (**3**), homogeneous by TLC: mp 51.4–52.5 °C; $[\alpha]D$ −0.90° (*c* 5.5 $CHCl_3$): ir ($CHCl_3$) 3000, 2960, 2860, 1450, 1415, 1370, 1345, 1310, and 1080 cm^{-1}; 60-MHz NMR[9] (CCl_4) δ 3.95 (m, 2 H, protons on the carbons bearing the halogens), 3.40, 320 (each 1 H, m, protons on carbons bearing oxygen), 2.67 (m, 2, methylene protons at C-4 of tetrahydropyran ring), 2.1–1.08 (m, 14 H), 0.95 (m, 6 H, terminal methyl group protons); mass spectrum (70 eV) *m/e* (rel intensity) 342 (2), 340 (6), 338 (5), 271 (14), 269 (53), 267 (37), 261 (4), 259 (10), 188 (16), 178 (13), 177 (20), 176 (15), 175 (59), 160 (10), 159 (9), 158 (24), 123 (97), 109 (13), 101 (37), 99 (19), 97 (33), 96 (42), 95 (16), 88 (22), 83 (93), 81 (88), 79 (12), 70 (40), 69 (55), 67 (84), 57 (25), 56 (32), 55 (100), 54 (22), 53 (25), 43 (76), 42 (20), 41 (94).

Anal. Calcd for $C_{15}H_{28}BrClO$: C, 52.87; H, 8.58; Br, 23.45; Cl, 10.40. Found: C, 53.47; H, 8.24; Br, 23.11; Cl, 10.09.

B. From Isodactylyne (2). Hydrogenation of 57.5 mg of **2** in the same manner as described above for **1** gave 36.7 mg (77.7%) of crude **3**. Recrystallization from 95% ethanol gave pure **3**, homogeneous by TLC: mp 51.0–52.5 °C; ir, NMR, and MS same as described in A above; mmp 51.5–53.3 °C; $[\alpha]D$ −0.90° (*c* 2.12, $CHCl_3$).

Acknowledgments. This work was supported in part by NIH Grants CA-12530 and 17256. We are grateful to the Lerner Marine Laboratory for the use of its facilities. We gratefully acknowledge grants from the National Science Foundation (GP 38410) and the Phillips Petroleum Co., Bartlesville, Okla., which aided in the purchase of NMR spectrometers and accessories.

Registry No.—**1**, 55306-12-2; **2**, 58001-90-4; **3**, 55229-33-9.

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(5) Cf. spectra of laurencin [T. Irie, M. Suzuki, and T. Masamune, *Tetrahedron*, **24**, 4193 (1968)] and laureatin [T. Irie, M. Izawa, and E. Kurosawa, *ibid.*, **26**, 851 (1970)].
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(8) Melting points are uncorrected. Infrared spectra were taKen on a Beckman IR-8 spectrophotometer and ultraviolet spectra on a Cary Model 118 spectrophotometer using 1-cm matched quartz cells. NMR spectra were acquired on Varian T-60 or XL-100 spectrometers in the solvents specified; signals are reported in parts per million (δ) downfield from internal tetramethylsilane. Mass spectra were obtained on a Hitachi RMU-7 spectrometer and optical rotations on Perkin-Elmer 141 digital readout or Gaertner polarimeters. Microanalyses were obtained from Mr. E. Meier, Department of Chemistry, Stanford University, Palo Alto, Calif. Chromatographic adsorbents used were Florisil (Fischer, 100–200 mesh) and silicic acid (Mallinckrodt, silicAR CC-7 and Brinkmann TLC mesh).
(9) For NMR data at 100 MHz ($CDCl_3$) see ref 2.

Quassimarin, a New Antileukemic Quassinoid from *Quassia amara*[1,2]

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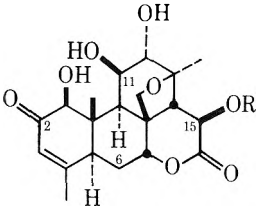
In the course of a continuing search for tumor inhibitors of plant origin, the sap of *Quassia amara* L.[3] (Simaroubaceae) was found to show significant activity in vivo against the P-388 lymphocytic leukemia in mice (PS) and in vitro against cells derived from human carcinoma of the nasopharynx (KB).[4] We report herein the fractionation of an active extract of *Q. amara* and the isolation and structural elucidation of a new antileukemic quassinoid,[5] quassimarin (**1**), and the companion quassinoid, simalikalactone D (**2**).



1, R = $COC(OAc)(CH_3)C_2H_5$
2, R = $COCH(CH_3)C_2H_5$

Fractionation of the dried sap, guided by assay against the KB and PS systems, revealed that the inhibitory activity was concentrated, successively, in the ethyl acetate layer of an ethyl acetate–water partition, the aqueous methanol layer of a 10% aqueous methanol–petroleum ether partition, and in the aqueous methanol layer of a 20% aqueous methanol–carbon tetrachloride partition. Column chromatography of the final aqueous methanol soluble material on SilicAR CC-7 yielded KB- and PS-active fraction D upon elution with 2% methanol in chloroform. Rechromatography of fraction D, first on silica gel 60 with isopropyl alcohol in dichloromethane as eluent, then on SilicAR CC-7 with acetone in hexane as eluent, gave quassimarin (**1**) and simalikalactone D (**2**).[6]

Elemental analysis and high-resolution mass spectrometry established a molecular formula of $C_{27}H_{36}O_{11}$ for quassimarin (**1**). The presence of an α-acetoxy-α-methylbutyrate ester was indicated by peaks in the mass spectrum at *m/e* 143 $[CO\text{-}C(OAc)(CH_3)C_2H_5]\cdot^+$, 115 $[C(OAc)(CH_3)C_2H_5]\cdot^+$, and 83 $[COC(CH_3)=CHCH_3]\cdot^+$, and by a dominant high mass fragment ion at *m/e* 358 corresponding to $M^+ - H_2O - HOOC\text{-}C(OAc)(CH_3)C_2H_5$. Furthermore, the NMR spectrum contained signals for primary, tertiary, and acetate methyl groups assignable to the ester. Lithium aluminum hydride reduction of **1** afforded 2-methyl-1,2-butanediol. A one-proton doublet at τ 3.52 (J = 14 Hz) in the NMR spectrum of **1** confirmed the point of ester attachment to be at C-15.[7]

Irradiation of the C-15 proton doublet at τ 3.52 led to the

assignment of the doublet of doublets at τ 7.66 (J = 14, 2 Hz) to the C-14 proton. Then irradiation of the latter peaks caused not only the collapse of the doublet at τ 3.52, but also sharpening of a broad singlet at τ 6.18 assigned to the C-12 proton. The long-range coupling between the C-12 and C-14 protons is in accord with an α configuration for the C-12 hydroxyl. The small coupling between the C-11 and C-12 protons suggests a β stereochemistry for the C-11 hydroxyl, since any flattening of the ring to relieve the strain caused by two axial hydroxyls could cause the dihedral angle between the C-11 and C-12 protons to approximate 90°.

A broad multiplet at τ 5.3, superimposed on two other proton resonances, was assigned to the C-11 proton. Addition of benzene to the chloroform solution of **1** resolved the three resonances into the C-11 proton multiplet, a doublet (J = 8 Hz) coupled with a broadened doublet at τ 6.43, both assigned to the C-30 protons, and a triplet (J = 3 Hz) assigned to the C-7 proton. Irradiation of the C-11 proton multiplet caused the collapse of an OH doublet (J = 7 Hz) at τ 6.82 as well as change in a signal at τ 7.8. The latter signal was assigned to the C-9 proton.

The uv spectrum and characteristic fragment ion[8] at m/e 151 in the mass spectrum of quassimarin (**1**) supported the formulation of the A-ring portion as shown. In addition, the NMR spectrum of **1** contained signals for a vinyl proton and a vinyl methyl as well as a sharp singlet at τ 5.83 assignable to the C-1 proton. The detection of a 6% nuclear Overhauser effect between the C-1 and C-9 protons confirmed the β stereochemistry of the C-1 hydroxyl.

Experimental Section

General. Melting points were determined on a Mettler Model FP2 hot stage and are uncorrected. Ultraviolet absorption spectra were determined on a Beckman Model DK-2A recording spectrophotometer. Infrared spectra were determined on Perkin-Elmer Model 257 and Model 337 recording spectrophotometers. Nuclear magnetic resonance spectra were determined on a Varian HA-100 spectrometer or a JEOL PS-100 pulsed FT NMR spectrometer interfaced to a Texas Instrument JEOL 980A computer, with tetramethylsilane as an internal standard. Mass spectra were determined on Hitachi Perkin-Elmer Model RMU-6E and AEI Model MS-902 spectrometers. Values of $[\alpha]_D$ were determined on a Perkin-Elmer Model 141 automatic polarimeter. Gas–liquid chromatography was carried out on a Varian Aerograph Model 1800 gas chromatograph equipped with a 9-ft column, packed with 18% QF on Chromosorb W, at a column temperature of 80 °C with helium as carrier gas. Microanalyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich. Petroleum ether refers to the fraction of bp 60–68 °C. All thin layer chromatography was carried out on ChromAR 7GF precoated glass plates (Mallinckrodt). Visualization of TLC was effected with short-wavelength uv and concentrated sulfuric acid–vanillin–ethanol (20:1:3) spray.

Extraction and Preliminary Fractionation. The dried sap (2 kg) of *Q. amara* was partitioned between water (12 l.) and ethyl acetate (3 × 8 l.). The combined ethyl acetate layers were evaporated to give a dark brown residue (A, 80 g). Fraction A was partitioned between 10% aqueous methanol (0.5 l.) and petroleum ether (5 × 0.3 l.). The aqueous methanol layer and combined petroleum ether layers were evaporated to give B (77 g) and C (3 g), respectively. Further partitioning of fraction B between 20% aqueous methanol (0.6 l.) and carbon tetrachloride (3 × 0.3 l.) afforded, after evaporation, fractions D (65 g) and E (12 g).

Fraction D was subjected to column chromatography (SilicAR CC-7, 1500 g) with chloroform followed by chloroform containing increasing amounts of methanol as eluents. Elution with 2% methanol in chloroform gave fraction F (6.1 g) which was further fractionated by column chromatography on silica gel 60 (500 g). Elution with 4% isopropyl alcohol in dichloromethane yielded fraction G (1.9 g). Fraction G was submitted to further column chromatography on SilicAR CC-7 (120 g). Elution with 25% acetone in hexane gave fractions H (0.33 g) and I (0.49 g).

Simalikalactone D (2). Fraction H was purified by preparative TLC on ChromAR using ethyl acetate–cyclohexane (2:1). Elution of the major uv-active band afforded a residue which gave needles upon crystallization from ethyl acetate–hexane (**2**, 0.089 g, 0.005%). The material was identified by comparison of its melting point, $[\alpha]_D$, and uv and NMR spectra with those reported for simalikalactone D,[6] and by comparison of its TLC and ir and mass spectra with those of an authentic sample.[9]

Quassimarin (1). Preparative TLC of fraction I on ChromAR using ethyl acetate–cyclohexane (2:1), followed by elution of the major uv-active band, gave a residue which crystallized as needles from ethyl acetate–hexane (**1**, 0.06 g, 0.003%): mp 237.5–238.5 °C dec; $[\alpha]^{26}D$ +22.4° (c 0.29, $CHCl_3$); uv max (EtOH) λ (ϵ) 239 nm (10 800); ir ($CHCl_3$) 2.82, 5.71, 5.99, 7.93, 9.01, 9.43, 9.76 μ; NMR ($CDCl_3$) τ 8.95 (3 H, t, J = 7 Hz, CH_2CH_3), 8.80 (3 H, s, 10-CH_3), 8.45 (3 H, s, 13-CH_3), 8.38 (3 H, s, 2′-CH_3), 8.05 (3 H, s, 4-CH_3), 7.92 [3 H, s, C(=O)-CH_3], 7.66 (1 H, dd, J = 14 and 2 Hz, 14-H), 6.82 (1 H, d, J = 7 Hz, 11-OH), 6.43, 5.31 (each 1 H, d, J = 8 Hz, CH_2O), 6.18 (1 H, s, 12-H), 5.83 (1 H, s, 1-H), 5.6 (1 H, br s, OH), 5.35 (1 H, t, J = 3 Hz, 7-H), 5.3 (1 H, m, 11-H), 3.89 (1 H, br s, 3-H), 3.52 (1 H, d, J = 14 Hz, 15-H); mass spectrum m/e 536.2257 (M^+, calcd for $C_{27}H_{36}O_{11}$, 536.2258), 518, 358.1407 (calcd for $C_{20}H_{22}O_6$, 358.1416), 340, 301, 165, 151, 143.0707 (calcd for $C_7H_{11}O_3$, 143.0708), 115, 83.

Anal. Calcd for $C_{27}H_{36}O_{11}$: C, 60.44; H, 6.76. Found: C, 60.54; H, 6.88.

2-Methyl-1,2-butanediol from Quassimarin (1). A suspension of lithium aluminim hydride (7.0 mg, 0.18 mmol) and quassimarin (**1**, 9.7 mg, 0.018 mmol) in ether (1.5 ml) was stirred at room temperature for 4 h. Excess reagent was decomposed with saturated sodium potassium tartrate solution, the precipitate was removed, and the filtrate was concentrated at reduced pressure. Preparative GC afforded 2-methyl-1,2-butanediol which was shown to be identical (NMR, mass spectra, mixture GC analysis) with a sample prepared by conventional methods.[10]

Registry No.—**1**, 59938-97-5; **2**, 35321-80-3.

References and Notes

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(2) This investigation was supported by research grants from the National Cancer Institute (CA-11718 and CA-12059) and the American Cancer Society (CI-102K), and contracts with the Division of Cancer Treatment, NCI, National Institutes of Health (NO1-CM-12099 and NO1-CM-67002).

(3) The water displaced sap was collected in Costa Rica in the spring of 1974. We thank Dr. M. S. Hudson for supplying the plant material, in accordance with the program developed by the National Cancer Institute.

(4) Tumor-inhibitory activity and cytotoxicity were assayed under the auspices of the National Cancer Institute, by the procedures described by R. I. Geran, N. H. Greenberg, M. M. McDonald, A. M. Schumacher, and B. J. Abbott [*Cancer Chemother. Rep., Part 3*, **3**, 1 (1972)].

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A Convenient Preparation of Methyl (*E*)- and (*Z*)-4,4-Dimethoxy-2-butenoates by Electrolyses of Furfuryl Alcohol, Furfural, and 2-Furoic Acid

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Alkyl 4,4-dialkoxy-2-butenoates have been recognized as powerful Michael acceptors in the syntheses of the plant antitumor agent camptothecin[1] and of 11-oxoprostaglandins[2] and also as an unusual Diels–Alder dienophile.[3] Several efforts to obtain 4,4-dialkoxy-2-butenoates by the ozonolysis of 1,3-dienoates and subsequent acetalization, giving the *E* isomer,[3] by the alcoholysis of 4-ethoxy-2-butenolide derived

Table I. Conditions and Results of Anodic Oxidation of 2-Substituted Furans and the Related Compounds

Run	Substrate (g)	Supporting[a] electrolyte	Current, A/cm²	Quantity of electricity, Faradays/mol	Temp, °C	Product yield, % 2a	2b	3a	3b	5
1	**1a** (3.00)	A	0.033	8.0	13–15			75		
2	**4** (1.00)	A	0.083	12.5	27–28			87		
3	**6** (1.00)	B	0.083	12.5	17–23			84		
4	**1b** (1.00)	A	0.033	8.0	15–19		72	24		
5	**1a** (1.00)	A	0.033	2.1	15–16	91				
6	**2a** (1.00)	A	0.066	6.0	19–20			66		
7	**4** (1.00)	A	0.083	2.1	18–20					71
8	**5** (1.00)	A	0.083	10.0	26–27			76		
9	**6** (1.00)	C	0.083	12.5	15–16			3[c]	81	

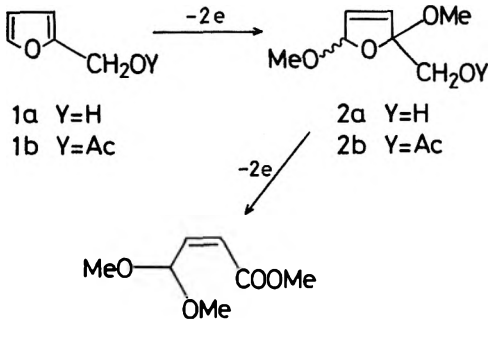
[a] A, Et_4NClO_4 (0.10 g); B, Et_4NClO_4 (0.10 g)–Et_3N (1.00 g); C, NH_4Br (0.10 g)–Et_3N (1.00 g). [b] Isolated yield. Yields are calculated on isolated product based on added starting material. [c] Based on GLC analysis: 10% SE-30 on Chamelite CK 80–100 (3 m × 4 mm) at 145 °C with a flow rate of 20 ml/min.

from photolysis of furfural, giving a mixture of *E* and *Z* isomers,[1,4] and by the Wittig reaction of glyoxal diethyl acetal with ylides, giving *E* isomer,[1a,5] have been recorded. As a consequence of our interest in the method of the electrochemical alkoxylation of 2-substituted furans,[6] we found the highly efficient and selective one-step synthesis of either *Z* or *E* isomer of methyl 4,4-dimethoxy-2-butenoates (**3a** and **3b**) by electrolyses of **1a**, **4**, and **6**.

Earlier reports of anodic methoxylation of furan derivatives are those involving the formation of the corresponding 2,5-dimethoxy-2,5-dihydrofurans in sufficient yield.[7] On the other hand, a few examples of converting furfural,[8] 2-furoic acid,[8b] methyl 5-substituted 2-furoates,[9] and methyl 2-thiophencarboxylate[10] into ring opening products, e.g., maleic acid and 4-oxo-2-butenoates, by electrolysis have been reported. However, direct electrosynthesis of alkyl 4,4-dialkoxy-2-butenoates from 2-substituted furans has not yet been realized.

Electrolyses of 2-substituted furans **1a**, **1b**, **4**, and **6** were carried out under a constant current by using two platinum foil electrodes. The reaction conditions and results are listed in Table I. As shown in runs 1, 2, and 3 (Table I) methyl (*Z*)-4,4-dimethoxy-2-butenoate (**3a**) was obtained by the electrolyses of furfuryl alcohol (**1a**), furfural (**4**), and 2-furoic acid (**6**) in 75–87% yields. In a similar condition, electrolysis of the acetate **1b** afforded the corresponding dihydrofuran **2b** as a major product (72%) along with **3a** (24%).

The coulometric studies of the electrolysis of **1a** revealed that under a current density of 0.02 A/cm² (Figure 1) the extent of formation of **2a** from **1a** appears to be approximately linear with 2.1 Faradays/mol of passed electricity. In this stage most of **1a** was electrolyzed. However, when the electrolysis was prolonged, further oxidation of **2a** gave rise to afford the



2-butenoate **3a** completely after passing a current of 4–6 Faraday/mol. The successful and selective conversion of **1a** into **2a** and/or **3a** could be achieved when the current density was controlled below 0.05 A/cm². If the electrolysis is carried

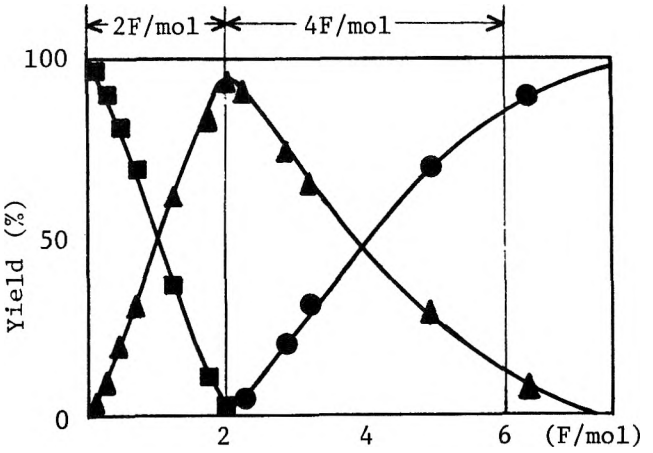
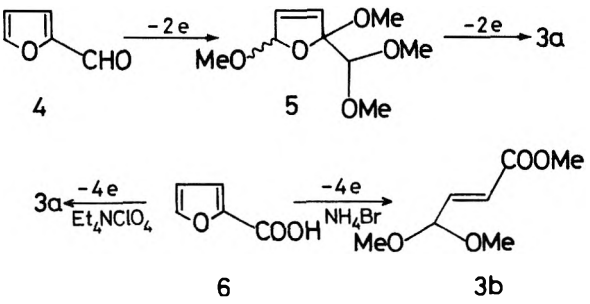


Figure 1. Current density 0.02 A/cm². Experimental points are given for **1a** (■), **2a** (▲), and **3a** (●).

out at a current of 0.2 A/cm², product selectivity is decreased (Figure 2). The conditions and results from stepwise electrolysis of **1a** and/or **2a** are also shown in runs 5 and 6. Electrolysis of furfural (**4**) in methanol under a constant current of 0.083 A/cm² gave 2-dimethoxymethyl-2,5-dimethoxy-2,5-dihydrofuran (**5**) in 71% yield after 2.1 Faradays/mol of current was passed (run 7). The formation of **3a** from **4** via **5**



could be rationalized by the electrolytic conversion of **5** to **3a** as shown in run 8. Electrolysis of the acid **6** using NH_4Br–Et_3N as an electrolyte resulted in *E* isomer **3b** preferably (run 9). The formation of **3b** would be caused by isomerization from **3a** to **3b** by the action of bromine radical,[11] which would be generated by one-electron oxidation of bromide ion on the anode.

A plausible mechanism of the anodic conversion of **2a** to **3a** is depicted in Scheme I. One-electron oxidation of **2a** would be considered to generate an alkoxy radical[12] which undergoes elimination of formaldehyde to give b. Successive one-electron oxidation of b and subsequent nucleophilic attack by meth-

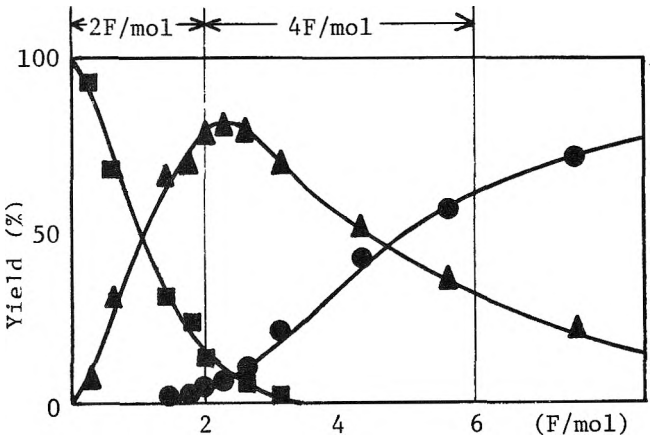
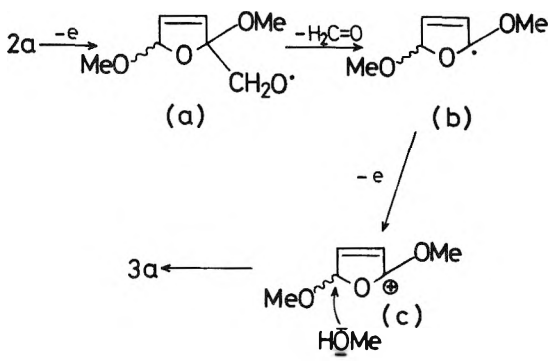


Figure 2. Current density 0.20 A/cm^2. Symbols follow: **1a** (■), **2a** (▲), and **3a** (●).

Scheme I



anol would produce the ring opening product **3a** via the cation intermediate c. In the course of the electrolysis two-electrons oxidation of formaldehyde is also expected to afford methyl formate. After all, the conversion of **2a** to **3a** should require four electrons on the anode. As shown in Figure 1, the conversion of ca. 80% of **2a** was achieved when 4 Faradays/mol of electricity was passed.

Experimental Section

All the boiling points are uncorrected. NMR spectra were recorded on a Hitachi R-24 spectrometer. Ir spectra were measured on neat liquids using a JASCO model IRA-1 spectrometer.

Materials. Commercially available furfuryl alcohol (**1a**) and furfural (**4**) were distilled under reduced pressure before use. 2-Acetoxymethylfuran (**2a**)[13] and 2-furoic acid (**6**)[14] were prepared according to the procedure described in the literature.

General Procedure of the Electrolysis. 2-Substituted furans **1a, 1b, 2a, 4, 5,** and **6** were dissolved in MeOH (20 ml) containing Et_4NClO_4, Et_4NClO_4–Et_3N, and/or NH_4Br–Et_3N as a supporting electrolyte. The solutions were electrolyzed under a constant current in a compartment cell equipped with two platinum foil electrodes (2 × 3 cm^2). The solution was condensed under reduced pressure, taken up in EtOAc, washed with aqueous $NaHCO_3$ and brine, and dried (Na_2SO_4). After evaporation of the solvent the residue was distilled by using a short-path distillation apparatus, to give the products **2a, 2b, 3a, 3b,** and **5.** The detailed reaction conditions and results of electrolyses of 2-substituted furans and the related compounds are listed in Table I. Analytically pure samples were obtained by column chromatography on silica gel with benzene–EtOAc (20/1).

2,5-Dimethoxy-2-hydroxymethyl-2,5-dihydrofuran (2a): bp 82–85 °C (7.5 mm) [lit.[15] bp 106–110 °C (18 mm)]; ir (neat) 3440 (OH), 2820 (CH_3O), 1633 cm^{-1} (C=C); NMR ($CDCl_3$) δ 2.68 (m, 1 H, OH), 3.15–3.72 (8 H, 2 CH_3O, CH_2O), 5.45–6.16 (3 H, CHO, CH=CH).

2-Acetoxymethyl-2,5-dimethoxy-2,5-dihydrofuran (2b): bp 105–109 °C (11 mm) [lit.[15] bp 117–119 °C (12 mm)]; ir (neat) 2820 (CH_3O), 1745 (C=O), 1632 cm^{-1} (C=C); NMR ($CDCl_3$) δ 2.07 (s, 3 H, CH_3CO), 3.15, 3.24 (2 s, 3 H, CH_3O), 3.43, 3.51 (2 s, 3 H, CH_3O), 3.88–4.48 (m, 2 H, CH_2O), 5.45–6.23 (3 H, CHO, CH=CH).

Methyl (*Z*)-4,4-Dimethoxy-2-butenoate (3a): bp 74–78 °C (12 mm); ir (neat) 2820 (CH_3O), 1728 (C=O), 1657 cm^{-1} (C=C); NMR ($CDCl_3$) δ 3.33 (s, 6 H, *gem*-CH_3O), 3.68 (s, 3 H, CH_3O), 5.68 (d, J = 7.2 Hz, 1 H, CH=), 5.87 (s, 1 H, CHO), 5.92 (d, J = 7.2 Hz, CH=).

Anal. Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.53; H, 7.64.

Methyl (*E*)-4,4-Dimethoxy-2-butenoate (3b):[3,4] bp 75–78 °C (12 mm); ir (neat) 2820 (CH_3O), 1726 (C=O), 1668 cm^{-1} (C=C); NMR ($CDCl_3$) δ 3.33 (s, 6 H, *gem*-CH_3O), 3.77 (s, 3 H, CH_3O), 4.96 (diffused d, J = 4.2 Hz, 1 H, CHO), 6.17 (diffused d, J = 16.2 Hz, 1 H, CH=), 6.76 (dd, J = 4.2, 16.2 Hz, 1 H, CH=).

2,5-Dimethoxy-2-dimethoxymethyl-2,5-dihydrofuran (5): bp 65–70 °C (7 mm) [lit.[15] bp 107–110 °C (13 mm)]; ir (neat) 2824 (CH_3O), 1632 (C=C), 1019, 1027, 978 cm^{-1}; NMR ($CDCl_3$) δ 3.18–3.52 (m, 12 H, CH_3O), 3.75–4.21 (1 H, CHO), 5.50–6.30 (m, 3 H, HC=CH, CHO).

Registry No.—**1a,** 98-00-0; **1b,** 623-17-6; **2a,** 19969-71-2; **2b,** 41991-02-0; **3a,** 57314-31-5; **3b,** 32815-00-2; **4,** 98-01-1; **5,** 59906-91-1; **6,** 88-14-2.

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A Novel Intermolecular Transfer Reaction of Alkenyltrialkylborates with Aqueous Bases and Its Application to the Protonolysis of Alkenylboron Derivatives

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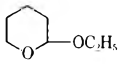
Conversion of organoboranes into organic products is most commonly achieved by either oxidation or protonolysis.[1] Whereas the alkaline hydrogen peroxide oxidation is a highly general reaction,[1] protonolysis with carboxylic acids suffers from a few difficulties, such as the incompatibility with various acid-sensitive functional groups and the frequent need for high temperatures (>100 °C).[2,3] In view of the growing significance of alkenylboron derivatives as synthetic intermediates, development of general and mild procedures for their protonolysis that are complementary to the existing acidic procedure is especially desirable.

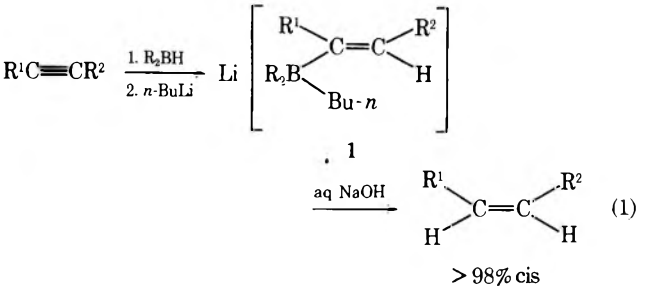
We have found that alkenyltrialkylborates (**1**), readily obtainable by the treatment of alkenyldialkylboranes with an alkyllithium reagent, undergo a selective protonolysis reaction

Table I. Reaction of Lithium Alkenyltrialkylborates (1) with Aqueous Sodium Hydroxide[a]

Entry	Alkenyltrialkylborate (1) R¹	R²	R	Registry no.	Product[b]	Registry no.	Yield,[c] %
1	*n*-C_4H_9	*n*-C_4H_9	c-C_6H_{11}	59643-33-3	*cis*-5-Decene	7433-78-5	92
2	*n*-C_4H_9	*n*-C_4H_9	Sia[e]	59643-34-4	*cis*-5-Decene		90
3	*n*-C_4H_9	*t*-C_4H_9	c-C_6H_{11}	59643-36-6	*cis*-2,2-Dimethyl-3-octene	59574-63-9	90
4	CH_3	*t*-$C_4H_9OC_2H_5$	c-C_6H_{11}	59643-39-9	*cis*-5-*tert*-Butoxy-2-pentene	59574-64-0	87
5	H	c-C_6H_{11}	c-C_6H_{11}	59643-38-8	Cyclohexylethene[f]	695-12-5	93
6	H	*t*-$C_4H_9OC_2H_5$	c-C_6H_{11}	59643-35-5	4-*tert*-Butoxy-1-butene[f]	22498-04-0	86
7	H		c-C_6H_{11}	59643-37-7	4-(2′-Tetrahydropyranyloxy)-1-butene[g]	59574-65-1	95

[a] Unless otherwise mentioned, the reaction was carried out over 48 h at ~25 °C. [b] All products except cyclohexylethene yielded satisfactory NMR, ir, and mass spectra. Cyclohexylethene was identified by GLC. [c] By GLC. [d] By isolation. [e] Sia = 3-methyl-2-butyl. [f] The reaction time was 12 h (25 °C). [g] Refluxed overnight.

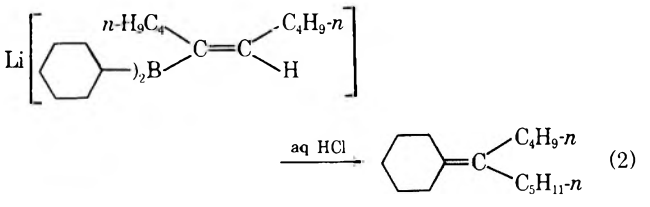
of the alkenyl groups with aqueous sodium hydroxide to produce the corresponding alkenes in excellent yields. The stereochemistry of the internal alkene product in each case has been found to be ≥98% cis by a combination of GLC, ^1H and ^{13}C NMR, and ir (absence of the trans band at ~970 cm^{-1}).



(1)

R^1 = alkyl or H; R^2 = alkyl

The basic protonolysis reported here is highly unique in that it appears to represent the first example of the conversion of alkenylborates into the corresponding alkenyl derivatives via coupling with electrophiles, i.e., proton, which proceeds with retention of all of the structural features of the alkenyl group of **1**. It should also be noted that treatment of the corresponding alkenyldialkylboranes with aqueous sodium hydroxide does not proceed at any appreciable rate under comparable reaction conditions. Moreover, treatment of the borate **1** with aqueous acids takes an entirely different reaction path from that shown in eq 1, undergoing an intramolecular carbon–carbon bond formation between the alkenyl and one of the alkyl groups (R).[4,5] For example, treatment of lithium 5-decenyldicyclohexyl (*n*-butyl)borate with hydrochloric acid produces nearly exclusively 5-cyclohexylidenedecane (eq 2). Only a trace amount of 5-decene is formed under these conditions.[4]



(2)

The mechanism of the basic protonolysis of **1** is, at present, not clear. An intuitively plausible mechanism which involves the dissociation of **1** into the corresponding alkenyllithium and trialkylborane does not appear to be operating. For treatment of **1** with another mole of *n*-butyllithium in a mixture of hexane and ether does not show any sign of exchange or displacement. Thus, the ^1H chemical shift and integration of the alkenyl proton of **1** as well as the ^1H chemical shift of the α protons of *n*-butyllithium (δ −1.1 ppm) remain unchanged on mixing **1** with *n*-butyllithium, the only noticeable change being a slow disappearance of *n*-butyllithium presumably owing to its reaction with ethyl ether.

In conclusion, alkenylboron derivatives can now be protonolyzed readily in a highly stereospecific manner to produce the corresponding alkenes under either acidic or basic conditions.

Experimental Section

5-Decyne, cyclohexylethyne, 3-butyn-1-ol, cyclohexene, isobutylene, dihydropyran, and *n*-butyllithium in hexane are all commercial reagents and used without further purification. Borane in THF was prepared as described in detail by Brown.[6] Infrared spectra were recorded on a Perkin-Elmer 137 spectrometer. ^1H and ^{13}C NMR spectra were recorded on Varian T-60A and Varian CFT-20 spectrometers, respectively. GLC analyses were performed on a Perkin-Elmer 3920 gas chromatograph using 6 ft × 0.125 in. o.d. 10% SE-30 and 10% Carbowax 20M columns.

General Procedure for the Protonolysis of Alkenyltrialkylborates. The following conversion of 5-decyne into *cis*-5-decene is representative. 5-Decyne (10 mmol) was hydroborated with 10 mmol of dicyclohexylborane[6,7] in THF (50 ml) at 0 °C. To this solutio were added, in sequence, 10 mmol of *n*-butyllithium in hexane (0 °C, 1 h) and 5 ml of 6 N sodium hydroxide. The reaction mixture was stirred vigorously at room temperature for 48 h.[8] GLC examination of the mixture, after oxidation with 30% hydrogen peroxide, indicated the presence of 9.2 mmol (92%) of 5-decene. After the alcoholic products and other impurities were removed by column chromatography on a short alumina (neutral) column using petroleum ether as a solvent, evaporation of the solvent provided 8.3 mmol (83%) of 5-decene (99% pure by GLC and 99% cis by ^{13}C NMR): ^1H NMR (CCl_4) δ 0.90 (t, J = 5 Hz, 6 H), 1.07–1.56 (m, 8 H), 1.71–2.25 (m with peaks at 1.97 and 2.06 ppm, 4 H), and 5.20 ppm (t, J = 5 Hz, 2 H); ^{13}C NMR [CCl_4, $(CO_3)_2CO$] δ 22.40, 31.13, 35.75, 40.91, and 138.60 ppm; ir (neat) 2900 (s), 2820 (s), 1650 (w), 1455 (s), 1445 (s), 1370 (m), 720 cm^{-1} (w).

The other olefin products were obtained in similar manners. Minor changes in reaction conditions are indicated in Table I.

4-*tert*-Butoxy-1-butyne and 5-*tert*-Butoxy-2-pentyne. 4-*tert*-Butoxy-1-butyne was prepared according to a literature procedure[9] by treating 3-butyn-1-ol in dichloromethane with an excess of isobutylene in the presence of an acid catalyst at room temperature. To 4-*tert*-butoxy-1-butyne in THF were added in sequence an equimolar amount of *n*-butyllithium and a threefold excess of methyl iodide at 0 °C. The reaction mixture was stirred overnight at room temperature. After addition of water, the mixture was extracted with diethyl ether and dried over $MgSO_4$. 5-*tert*-Butoxy-2-pentyne obtained quantitatively after removal of the volative substances was sufficiently pure by GLC and ^1H NMR and was used without further purification: ^1H NMR (CCl_4) δ 1.15 (s, 9 H), 1.72 (t, J = 2 Hz, 3 H), 2.18 (tq, J = 7 and 2 Hz, 2 H), and 3.34 ppm (t, J = 7 Hz, 2 H).

4-Tetrahydropyranyloxy-1-butyne. To 400 mmol of dihydropyran, freshly distilled from sodium hydroxide pellets, were added four drops of concentrated hydrochloric acid and 100 mmol of 3-butyn-1-ol. The reaction mixture was initially cooled in an ice bath and was then allowed to stand for 3 h at room temperature. After

addition of 40 ml of diethyl ether, the mixture was washed with 30 ml of 10% NaOH, dried over $MgSO_4$, and distilled to provide the title compound quantitatively: bp 51 °C (2 mm); $n^{23}D$ 1.4559; ^1H NMR (CCl_4) δ 1.2–1.76 (m, 6 H), 1.87 (t, J = 2 Hz, 1 H), 2.40 (td, J = 7 and 2 Hz, 2 H), 4.06 (m, 4 H), and 4.60 ppm (s, 1 H); ir (neat) 3235 (s), 2910 (s), 2840 (s), 2110 cm^{-1} (w).

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work and the National Science Foundation for an instrument grant (MPS75-06106). We also thank Mr. Albert A. Kruger, who partially carried out anexperiment in Table I (entry 3).

Registry No.—5-Decyne, 627-19-0; 4-*tert*-butoxy-1-butyne, 59574-66-2; 5-*tert*-butoxy-2-pentyne, 59574-67-3; 4-tetrahydropyranyloxy-1-butyne, 40365-61-5; dihydropyran, 110-87-2; 3-butyn-1-ol, 927-74-2; 2,2-dimethyl-3-octyne, 19482-57-6; cyclohexylethyne, 931-48-6.

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(5) For related results obtained under nonaqueous conditions, see G. Zweifel and R. P. Fisher, *Synthesis*, 339 (1974).
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Preparation of Cyanoformates. Crown Ether Phase Transfer Catalysis

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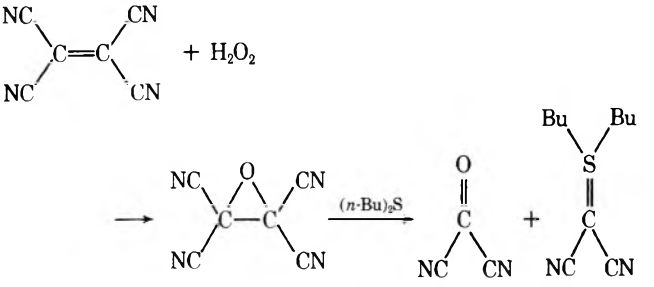
While the chemistry of chloroformates is extensive, that of cyanoformates is not. Thermal decomposition of primary alkyl chloroformates leads to alkyl chlorides and carbon dioxide at reasonable temperatures (150–200 °C).[1-3] By comparison, benzyl cyanoformate decomposes smoothly at 700 °C in the gas phase to yield benzyl nitrile and carbon dioxide.[4] The cyano group of cyanoformates can function as a dienophile in Diels–Alder reactions. For example, reaction of tetraphenylcyclopentadienone with phenyl cyanoformate yields 3,4,5,6-tetraphenylpyridine-2-carboxylic acid after hydrolysis.[5] Photolysis of ethyl cyanoformate in the presence of alkenes yields oxetanes. For example, photolysis of ethyl cyanoformate in 1,1-diphenylethylene yields 2-cyano-2-ethoxy-3,3-diphenyloxetane.[6] Photolysis of ethyl cyanoformate in cyclohexane yields products which may be rationalized as arising from primary cyano and ethoxycarbonyl radicals: cyclohexyl cyanide and ethyl cyclohexanecarboxylate respectively.[7,8] Finally, *tert*-butyl cyanoformate reacts with amino acids to yield *N*-*tert*-butyloxycarbonyl derivatives which are useful in peptide synthesis[9,10].

Table I. Preparation of Cyanoformates by Phase Transfer Catalysis

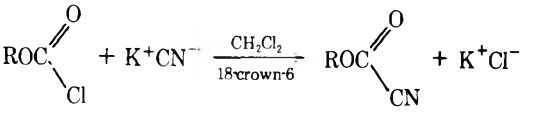
R	Yield, %	Bp, °C (mm)	Lit. bp, °C (mm)	Ref
Methyl	76	95–96 (760)	99 (760)	4
Ethyl	72	115–116 (760)	117 (760)	4
n-Butyl	90	55–56 (25)		
Isobutyl	94	52–53 (20)		
2,2,2-Trichloroethyl	88	100 (25)		
Isopropyl	62	36–37 (25)	35 (20)	11
2-Octyl	88	113–114 (25)		
Cyclohexyl	90	96–97 (20)	43 (1)	11
Benzyl	65	66–67 (0.6)	80 (2.5)	4
Phenyl	82	52–53 (mp)	51.6–53 (mp)	4, 11

The apparent lack of interest in this class of compounds may be due to difficulty in their synthesis. Benzyl, methyl, and ethyl cyanoformates have been prepared (~30% yield) by reaction of the corresponding alkyl chloroformates with powdered sodium cyanide.[4] Far better yields (70–90%) have been reported for the reaction of carbonyl cyanide with a wide variety of alcohols.[11] Unfortunately, carbonyl cyanide is not a commercially available reagent. It can be prepared (~60% yield) in two steps starting from tetracyanoethylene.[12,13] However, the price of tetracyanoethylene makes this a costly procedure.



An alternative preparation of *tert*-butyl cyanoformate involves several steps.[9] Recently, trimethylsilyl cyanide has been shown to react with methyl and ethyl chloroformates to yield the corresponding cyanoformates.[14] However, a drawback to this latter procedure is the necessity to prepare trimethylsilyl cyanide.[15-17]

We should like to report that cyanoformates can be prepared in good to excellent yields by the 18-crown-6[18] catalyzed reaction of potassium cyanide with the corresponding chloroformates in dichloromethane solvent. This is an example



of solid–liquid phase transfer catalysis.[17,19-21] The reaction is also related to the preparation of benzoyl cyanides by reaction of benzoyl chlorides with cyanide ion under PTC conditions.[22] The preparation of cyanoformates is a cleaner reaction, since no formation of dimers which was a major side reaction in the preparation of benzoyl cyanides under PTC conditions was observed to occur. The reaction is quite general and is successful for primary, secondary, benzyl, and phenyl cyanoformates (see Table I). Isolated yields of distilled cyanoformates are reported. The reaction, however, fails for the case of *tert*-butyl cyanoformate. This may be due to the well-known instability of *tert*-butyl chloroformate.[23] Also attempts to prepare carbonyl cyanide directly by the PTC reaction of potassium cyanide with phosgene failed under a wide variety of experimental conditions.

We hope that this new synthetic procedure will stimulate interest in cyanoformates.

Experimental Section

Many of these cyanoformates are known compounds; however, spectral properties even on those that are known are meager. For this reason, ir and NMR spectra of all compounds are reported here. The new cyanoformates, *n*-butyl, isobutyl, 2,2,2-trichloroethyl, and 2-octyl, have been analyzed. 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 spectrometer. Ten percent solutions in carbon tetrachloride with tetramethylsilane as internal standard were used. Vapor phase chromatography was carried out on a Hewlett-Packard F & M 700 using a 20% polyphenyl ether on Chromosorb P 4 ft × 0.25 in. column. Microanalysis was performed by Elek Microanalytical Laboratories, Torrance, Calif. Boiling points and melting points were not corrected.

Preparation of Isobutyl Cyanoformate. In a 50-ml round-bottom flask equipped with a reflux condenser, nitrogen inlet, and a Teflon-covered magnetic stirring bar was placed 30 ml of methylene chloride, 3.5 g (0.054 mol) of potassium cyanide, 6.8 g (0.05 mol) of isobutyl chloroformate (Eastman), and approximately 50 mg (0.02 mmol) of 18-crown-6.[18] The mixture was stirred at room temperature. The reaction could be followed by ir (the disappearance of the band at 1790 cm^{-1} due to the C=O of the starting chloroformate and the appearance of bands at 2250 cm^{-1} due to the C≡N and at 1750 cm^{-1} due to the C=O of the product cyanoformate) or by GLC (the starting material had a shorter retention time than the product cyanoformate in all cases which were examined). When the starting material had disappeared (~4 h), the solution was filtered. The solution was distilled through a 15-cm Vigreux column. Solvent was removed at atmospheric pressure. A fraction consisting of pure isobutyl cyanoformate by GLC, 6.0 g (0.047 mol), 94% yield, distilled at 52–53 °C (20 mm): NMR d (2 H) δ 4.1, J = 7 Hz, m (1 H) 2.1, d (6 H) 1.0, J = 7 Hz; ir 2250 C≡N, and 1750 cm^{-1} C=O. Anal. Calcd for $C_6H_9O_2N$: C, 56.68; H, 7.14. Found: C, 56.70; H, 7.03.

All other cyanoformates reported were prepared in analogous fashion.

Methyl cyanoformate from methyl chloroformate (Aldrich): NMR s (3 H) δ 4.0; ir 2250 C≡N, 1750 cm^{-1} C=O.

Ethyl cyanoformate from ethyl chloroformate (Aldrich): NMR q (2 H) δ 4.4, J = 7 Hz, t (3 H) 1.4, J = 7 Hz; ir 2250 C≡N, and 1750 cm^{-1} C=O.

***n*-Butyl cyanoformate** from *n*-butyl chloroformate (Aldrich): NMR t (2 H) δ 4.4, J = 7 Hz, multiplets (7 H) 1.7–1.0; ir 2250 C≡N, and 1750 cm^{-1} C=O. Anal. Calcd for $C_6H_9O_2N$: C, 56.68; H, 7.14. Found: C, 57.01; H, 7.10.

2,2,2-Trichloroethyl cyanoformate from 2,2,2-trichloroethyl chloroformate (Aldrich): NMR s (2 H) δ 4.75; ir 2250 C≡N, and 1760 cm^{-1} C=O. Anal. Calcd for $C_4H_2O_2NCl_3$: C, 23.73; H, 1.00. Found: C, 23.87; H, 1.32.

Isopropyl cyanoformate from isopropyl chloroformate (Research Organic/Inorganic Chemical Co.): NMR septet (1 H) δ 5.2, J = 7 Hz, d (6 H) 1.4, J = 7 Hz; ir 2250 C≡N, 1750 cm^{-1} C=O.

2-Octyl cyanoformate from 2-octyl chloroformate which had been prepared by reaction of 2-octyl alcohol with phosgene:[24] NMR m (1 H) δ 5.1, m (16 H) 1.3; ir 2250 C≡N and 1745 cm^{-1} C=O. Anal. Calcd for $C_{10}H_{17}O_2N$: C, 65.54; H, 9.35. Found: C, 65.51; H, 9.31.

Cyclohexyl cyanoformate from cyclohexyl chloroformate which had been prepared by reaction of cyclohexanol with phosgene:[24] NMR br (1 H) δ 5.0, m (10 H) centered at 1.6; ir 2245 C≡N, and 1745 cm^{-1} C=O.

Benzyl cyanoformate from benzyl chloroformate (Aldrich): NMR s (5 H) δ 7.2, s (2 H) 5.0; ir 2245 C≡N, and 1745 cm^{-1} C=O.

Phenyl cyanoformate from phenyl chloroformate (Eastman): NMR m (5 H) δ 7.3; ir 2250 C≡N, and 1760 cm^{-1} C=O.

Acknowledgments. This work was supported by a grant from the National Science Foundation, GP-40331X. M. E. Childs thanks the Stauffer Chemical Co. for a fellowship.

Registry No.—Isobutyl cyanoformate, 59873-30-2; isobutyl chloroformate, 543-27-1; methyl cyanoformate, 17640-15-2; methyl chloroformate, 79-22-1; ethyl cyanoformate, 623-49-4; ethyl chloroformate, 541-41-3; *n*-butyl cyanoformate, 5532-84-3; *n*-butyl chloroformate, 592-34-7; 2,2,2-trichloroethyl cyanoformate, 59873-31-3; 2,2,2-trichloroethyl chloroformate, 17341-93-4; isopropyl cyanoformate, 59873-32-4; isopropyl chloroformate, 108-23-6; 2-octyl cyanoformate, 59873-33-5; 2-octyl chloroformate, 15586-11-5; cyclohexyl cyanoformate, 5532-84-4; cyclohexyl chloroformate, 13248-54-9; benzyl cyanoformate, 5532-86-5; benzyl chloroformate, 501-53-1; phenyl cyanoformate, 5532-82-1; phenyl chloroformate, 1885-14-9; potassium cyanide, 151-50-8.

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An Unusual Arene Oxide Reaction. Solvent Capture during Acid-Catalyzed Solvolysis of 7,12-Dimethylbenz[a]anthracene 5,6-Oxide

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Recent interest in polycyclic arene oxides as mediators of polycyclic arene carcinogenesis[2] has prompted us to study the aqueous solvolysis of 7,12-dimethylbenz[*a*]anthracene 5,6-oxide (1), a K-region[3] metabolite[4] of the carcinogenic 7,12-

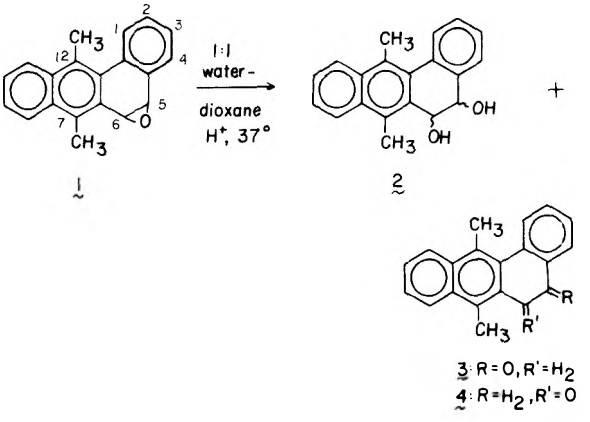


Table I. Product and Rate Data for the Reaction of 7,12-Dimethylbenz[a]anthracene 5,6-Oxide (1) in Acidic 1:1 Dioxane-Water (v/v), 0.10 M in KCl at 36.8 °C

Reaction pH[a]	$k_{obsd} \times 10^4$, s^{-1}	Yield[b] % 5 + 6 ketones	Cis dihydrodiols	Trans dihydrodiols
1.0		25	8	67
3.0		24	9	67
5.0		20	11	69
5.50	22.2	27	10	63
5.90	12.4	25	9	66
6.20	5.67			
6.60	2.44	33	16	51
7.0		25	14	61

[a] By glass electrode. [b] Integration of HPLC traces with correction for ϵ_{254} values.

Table II. Comparison of the Product and Rate Data on 7,12-Dimethylbenz[a]anthracene 5,6-Oxide with Related Benz[a]anthracene Oxides Not Containing Bay-Position Methyl Groups. Reactions Conducted in 1:1 Dioxane-Water 0.10 M in KCl at 37 °C

K-Region arene oxide	k_H,[c] $M^{-1} \times 10^{-1}$	Dihydrodiol yield, %	Cis/trans ratio of dihydrodiols	Rearrangement products
Benz[a]anthracene 5,6-oxide (5)[a]	1.5	25	31/69	Phenols
3-Methylcholanthrene 11,12-oxide (6)[a]	99	25	75/25	Phenols
7,12-Dimethylbenz-[a]anthracene 5,6-oxide (1)[b]	90	75	15/85	Ketones

[a] Data from ref 5. [b] Data from this work. [c] Specific acid catalyzed rate constant.

dimethylbenz[a]anthracene. We report here that in acid-catalyzed reactions, oxide 1 shows unusually high electrophilicity toward water, as compared to several previously studied K-region arene oxides.[5] Treatment of 1 with aqueous dioxane containing dilute acid produced mostly K-region dihydrodiols, 2, along with some K-region ketones, 3 and 4. In contrast, we previously found that under the same conditions the K-region oxides of phenanthrene, benz[a]anthracene (5), dibenz[a,h]anthracene, and 3-methylcholanthrene (6) all gave high yields of K-region phenols with lesser amounts of K-region dihydrodiols.[5]

Oxide 1 was maintained at constant pH with dilute HCl in a pH stat at 37 °C in 1:1 dioxane–water (v/v), 0.10 M in KCl. After all the oxide had reacted, the products were analyzed by high-pressure liquid chromatography (HPLC). Eluted peaks were identified as K-region dihydrodiols, 2, and ketones, 3 and 4, by comparison of their retention volumes and ultraviolet spectra with those of authentic samples.[6-9] HPLC of the ketones from reaction of oxide 1 at pH 5.0 showed that the 5 ketone, 3, and the 6 ketone, 4, were produced in the ratio of 2:3, respectively. Product yields as a function of pH are summarized in Table I. Control experiments showed that under these reaction and analysis conditions the dihydrodiols are stable. The 75% yield of dihydrodiols is strikingly different from the 25% dihydrodiol yields we obtained from the reaction of several other arene oxides.[5] The cis/trans ratio of the dihydrodiols obtained from 1 was 15/85; this is much lower than that obtained from 3-methylcholanthrene 11,12-oxide

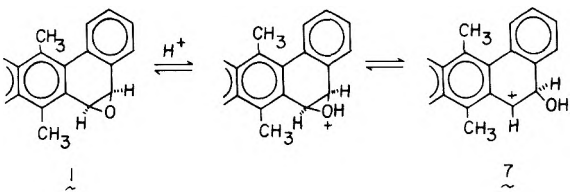
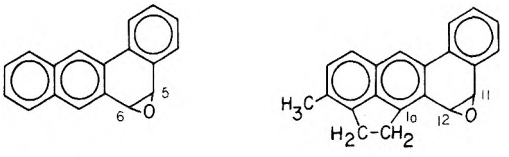


Figure 1. Generation of a benzylic cation, 7, by reversible protonation of the oxirane oxygen followed by scission of the C_6–O bond.

(6), and is even lower than that obtained from benz[a]anthracene 5,6-oxide (5) (Table II). K-Region phenols, the major solvolysis product of the previously studied oxides,[5] could not be detected.



5 6

The kinetics of the solvolysis reaction at 36.8 °C were monitored spectrophotometrically. The k_{obsd} values for the first-order disappearance of oxide 1 are proportional to $[H^+]$ in the pH range 5–7 (Table I); the proportionality constant k_H is 900 M^{-1} s^{-1}. The pH–rate profile in this pH range is nearly identical with that of 3-methylcholanthrene 11,12-oxide (6),[5,10] and is consistent with reversible protonation of the oxirane oxygen, followed by rate-limiting ring opening to an intermediate cation (for example, 7 in Figure 1).[5,11] Product formation then occurs rapidly either by attack of water or rearrangement, followed by proton loss.

The formation of cations analogous to 7 from different arene oxides occurs at different rates, according to the ability of the attached aryl groups to stabilize the incipient positive charge at the benzylic carbon.[5] It was shown in our previous work that there was a positive correlation between the k_H value for a given oxide and the cis/trans ratio of the product dihydrodiols.[5] This is so because of the large amount of positive charge delocalized throughout the carbons of both the rate-limiting ring opening and the cis-addition transition states, whereas the positive charge density on the carbons of the trans-addition transition state is much lower.[5] Thus, solvolysis of 7,12-dimethylbenz[a]anthracene 6-oxide (1) would, on electronic grounds, be expected to produce nearly the same cis/trans ratio as 6. In fact, however, the ratio from 1 is 15-fold lower.

We have previously observed K-region dihydrodiols as products of acid-catalyzed solvolysis of arene oxides in 1:1 dioxane–water, 0.10 M in KCl.[5] In solvent water at pH 6–7, phenanthrene 9,10-oxide and several alkylated benzene oxides also produce high yields of dihydrodiol.[12,13] The trans dihydrodiol yields reported here, which are higher than we previously found,[5] may be related to the strain inherent in the 7,12-dimethylbenz[a]anthracene 5,6-oxide system. Glusker et al.[14] have shown by x-ray diffraction that in the crystal, the phenyl ring of oxide 1 (carbon 1–4, 1a, and 4a) is twisted such that there is a dihedral angle of 28° between the phenyl and naphthyl rings (Figure 2). This twist may have two related effects: (1) it may cause the observed high rate of acid-catalyzed ring opening due to increased strain in the oxirane ring, and (2) it may largely prevent cis attack of water due to decreased conjugative interaction between the K-region carbons and the aryl moieties.

The dihedral twist present in the ions from 1 may cause the observed low yield of rearrangement products by retarding the NIH shift,[15] because the twist may inhibit full cyclic

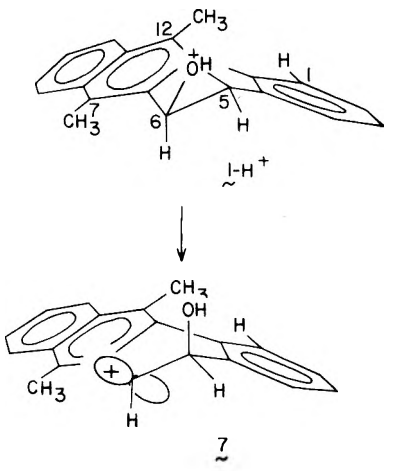


Figure 2. Formation of cation 7 from the twisted arene oxide 1.

conjugation in the NIH shift transition state,[5] or cause the reacting C–H bond to overlap less with the adjacent empty p orbital.

The production of K-region ketones instead of phenols from solvolysis of 1 is a related phenomenon. Most arene oxides would be expected to rearrange by the NIH shift to ketones and rapidly tautomerize to the more stable phenolic form.[15] Phenols are usually more stable because the endocyclic double bond becomes delocalized as a result of conjugation with the neighboring aromatic groups.[16] However, in the case of 5- and 6-hydroxy-7,12-dimethylbenz[*a*]anthracenes, the noncoplanarity of the K-region endocyclic bond with the attached aryl groups should inhibit the full cyclic delocalization required for phenol stability.[9,17] Indeed, it has been found that the 5 and 6 ketones are more stable than the respective phenols, and that the phenol–ketone tautomerization occurs only under conditions much more vigorous than we used (at 90 °C in 0.01 M HCl, $t_{1/2}$ = 10 h).[8] Thus, ketones **3** and **4** are primary products of solvolysis that are formed by NIH shifts of cationic intermediates, but do not undergo the usual tautomerization because of steric destabilization of the phenols. In contrast, the phenols derived from rearrangement of benz[*a*]anthracene 5,6-oxide (**5**) and 3-methylcholanthrene 11,12-oxide (**6**) are more stable than the respective ketones because the nearly planar aromatic ring systems[18,19] allow delocalization of the endocyclic K-region double bonds.

The foregoing results illustrate the profound effects which a substituent distal to the oxirane ring can have on the solvolytic reactivity of an arene oxide. However, the relationship of these results to the biological effects of 7,12-dimethylbenz[*a*]anthracene 5,6-oxide or its parent hydrocarbon remains to be determined.

Experimental Section

Materials. Dioxane was purified by the method of Fieser.[20] It was mixed with an equal volume of double-distilled water, 0.200 M in KCl, sealed under nitrogen in 250-ml bottles, and stored at −20 °C. All other solvents were Spectrograde or were distilled before use. *cis*-5,6-Dihydro-5,6-dihydroxy-7,12-dimethylbenz[*a*]-anthracene was synthesized by osmium tetroxide oxidation of the parent hydrocarbon;[17] *trans*-5,6-dihydro-5,6-dihydroxy-7,12-dimethylbenz[*a*]-anthracene was synthesized by lithium aluminum hydride reduction of the 5,6-quinone in ether followed by column chromatographic separation (Florisil and benzene–ethanol) of the cis and trans dihydrodiols.[17] The oxide, **1**, was synthesized by treatment of the trans dihydrodiol with dimethylformamide dimethyl acetal in benzene at reflux.[17] The K-region ketones were synthesized by dehydration of the cis dihydrodiol in refluxing acetic acid–HCl, followed by Florisil–benzene column chromatography.[8]

Spectra. Uv spectra were recorded on a Cary 15 spectrophotometer.

High-Pressure Liquid Chromatography. A Du Pont Model 830 chromatograph equipped with a Zorbax (silica) column (0.25 m × 2.2 mm i.d.) and a 254-nm photometric detector was used. Elution of a reaction aliquot with 1:1 (v/v) hexane–(dichloromethane, 2-propanol, acetic acid; 1000:20:0.1) produced peaks at 8 ml (ketones **3** and **4**), 35 ml (cis dihydrodiol), and 80 ml (trans dihydrodiol). Integration was by multiplication of peak height by peak width at half height; a correction for the different ϵ value at 254 nm was applied for the ketone peak.[8] Elution of a reaction aliquot with the upper layer of 25:1:0.2 (v/v) hexane–dioxane–formic acid produced peaks due to the 6 ketone, **4** (2.4 ml) and the 5 ketone, **3** (2.8 ml), in addition to the dihydrodiol peaks.

Rate Measurements. Kinetics were performed similarly to previous experiments.[5] Reactions were run in a 20-ml stirred reactor thermostated at 36.8 ± 0.05 °C and kept at constant pH by a Radiometer pH stat. Aliquots were removed by automatic pipet and immediately quenched in dioxane–water containing sodium bicarbonate. The absorbance of each quenched aliquot was read at 277.0 nm, a λ_{max} of oxide **1**; rate constants were obtained graphically from plots of ln $(A_t - A_\infty)$ vs. time.

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Registry No.—**1**, 39834-38-3; *cis*-**2**, 2518-02-7; *trans*-**2**, 16644-15-8; **3**, 53306-07-3; **4**, 55327-65-6.

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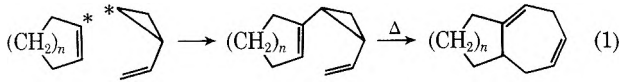
A Facile Route to Divinylcyclopropanes. An Efficient Method for the Annelative Formation of Functionalized Cycloheptanes

Summary: The reaction of *cis*- and *trans*-1-lithio-2-vinylcyclopropanes with 3-alkoxyenones provides an efficient, stereospecific route to various *cis*- and *trans*-1,2-divinylcyclopropanes and rearrangement of the latter compounds allows for the overall annelative formation of functionalized cycloheptanes; extension of this study to the preparation of cyclohept-4-enones is exemplified by the synthesis of karahanaenone.

Sir: The paucity of general methodology for the direct formation of functionalized seven-membered carbocycles and the occurrence of such ring systems in an increasing number of natural products[1] of biological importance has prompted our interest in developing methods which would provide for the efficient annelative formation of functionalized cycloheptanes. In connection with our synthetic objectives, an annelation strategy was sought which, from a topological viewpoint, would allow for the conjunction of a five-carbon synthon and an appropriately functionalized two-carbon unit. As outlined in eq 1, this objective could be realized through

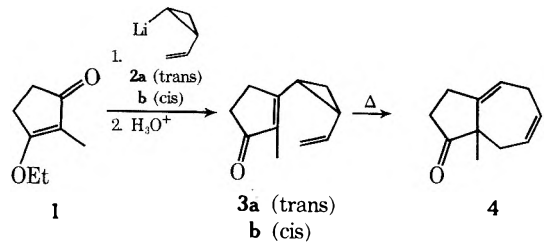


(1)

the attachment of a suitably activated vinylcyclopropane to a double bond or its latent equivalent to form a divinylcyclopropane subunit which upon thermal rearrangement[2] would be expected to afford the desired annelated product possessing strategically located functionality for subsequent synthetic utilization. The effectiveness of this sequence is contingent upon the development of a facile route to the divinylcyclopropane intermediate for which only limited and frequently circuitous methodology is available. This communication describes an efficient and operationally straightforward route to divinylcyclopropanes and applications of this method in synthesis.

Attention was initially focused on the reaction of 1-lithio-2-vinylcyclopropanes with 3-alkoxyenones (Scheme I) owing

Scheme I

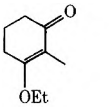
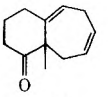
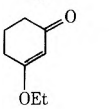
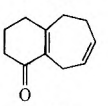
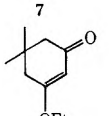
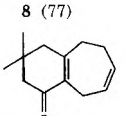
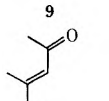
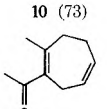
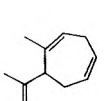


to the availability of the starting materials and the potential of the resulting functionality in subsequent synthetic operations. As such, *trans*-1-bromo-2-vinylcyclopropane[3] was converted to the lithiocyclopropane **2a** by reaction with *tert*-butyllithium (*t*-BuLi) in ether–pentane solvent at −78 °C. Addition of 3-ethoxy-2-methylcyclopent-2-enone (**1**) to this solution followed by hydrolysis of the reaction mixture with aqueous hydrochloric acid provided in high yield the *trans*-divinylcyclopropane product **3a**.[4,5] In a similar fashion, the reaction of reagent **2b**[3] with enone **1** afforded exclusively the *cis*-divinylcyclopropane product **3b**.[5-7] In accord with studies on the configurational stability of lithiocyclopropanes,[8] the above results indicate that the stereochemistry of the 1-bromo-2-vinylcyclopropanes is retained during the course of the metallation, addition, and hydrolysis reactions.

The viability of the second step of the annelation sequence became apparent when it was found that a pure sample of *cis*-divinylcyclopropane **3b** (ir 1695 cm^{-1}), which had been stored in a sealed vial for several days at ambient temperature, gradually became enriched in a second component (ir 1740 cm^{-1}). Moreover, attempted distillation of **3b** provided in excellent yield a single compound (ir 1740 cm^{-1}) which was subsequently established as the desired annelated product **4**.[5,9] Furthermore, the thermolysis of the *trans*-divinylcyclopropane **3a** [in solution (sealed tube) or neat] also provided dienone **4** in high yield. As anticipated from earlier studies on the divinylcyclopropane rearrangement[2] and in further support of the above stereochemical assignments of the divinylcyclopropanes, the cis compound **3b** rearranges with a half-life of 30 min at 80 °C (10% CCl_4 solution, sealed Pyrex tube) while the trans isomer **3a** has a half-life of 38 min at 160 °C (10% CCl_4 solution, sealed Pyrex tube).

A particularly attractive feature of the above method is that the entire annelation sequence can be performed in one synthetic operation, i.e., initial reaction (1,2 addition of the reagent), acidic workup (formation of the divinylcyclopropane), and distillation (rearrangement and purification). As shown in Table I, the annelation sequence is readily extended to various cyclic and acyclic 3-alkoxyenones. While substitution on the 3-alkoxyenone has no effect on the overall efficiency of the sequence, ketones **7**, **9** and **11** afford annelated products resulting from isomerization of the proximate β,γ-unsaturated product of the rearrangement under the conditions of the thermolysis.

Table I

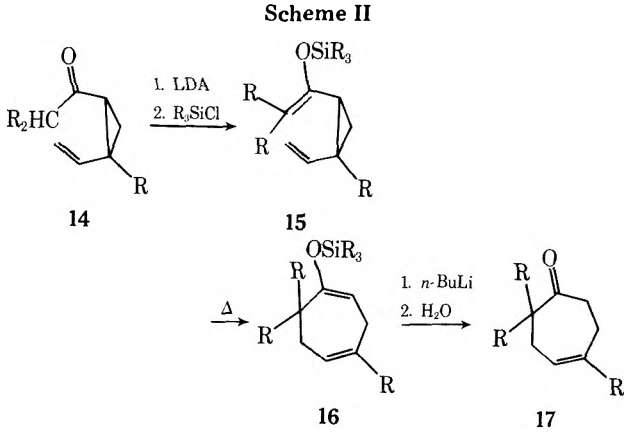
3-Alkoxyenone	Annelated product[5] (overall yield)[a]
1	4 (72)
 5	 6 (74)
 7	 8 (77)
 9	 10 (73)
 11	 12  13 (72)

[a] Yield of purified product based on 3-alkoxyenone.

A typical procedure for the above sequence is described below for the conversion of alkoxyenone **1** to ketone **4**. To a −78 °C ether (80 ml) solution of 1-bromo-2-vinylcyclopropane (40 mmol, 7:3 mixture of cis and trans) was added *t*-BuLi (48 mmol, 1.5 M in pentane) over 5 min. The resulting solution was stirred for 1.5 h at −78 °C and subsequently warmed to 0 °C. An ether (10 ml) solution of alkoxyenone **1** (20 mmol) was then added over a period of 2 min. The reaction mixture was stirred for 15 min at 0 °C and 15 min at ambient temperature and then carefully poured into a separatory funnel containing 2 N HCl (100 ml). Intermittent agitation of the above mixture (15 min) followed by standard workup provided in 91% yield (90% purity) the divinylcyclopropanes **3a** and **3b** (7:3 mixture of cis and trans), which were purified by silica gel chromatography (ether–hexane, 3:7).[7] Compounds **3a** and **3b** (2 M benzene solution) upon thermolysis (170–180 °C, 2 h) in a sealed Pyrex tube provided after purification ketone **4** (bp 54–59 °C, 0.15 mm) in 87% yield. Alternatively ketone **4** can be prepared by heating (250 °C, 5 min) the crude mixture of compounds **3a** and **3b** in a distillation apparatus followed directly by distillation of ketone **4**. In either case the method offers an exceptionally straightforward route to the annelated product with an overall yield of 72%.

The above strategy could be readily extended to other cycloheptane systems by varying the starting substrate (latent double bond equivalent). For example, aldehydes could be readily converted to acylvinylcyclopropanes **14** which could be used in the preparation of cyclohept-4-enones as outlined in Scheme II.

Scheme II



In order to test the efficacy of this route to cycloheptenones and examine variations in the lithio reagents, we have investigated this strategy in an approach to karahanaenone (**17**, R = Me).[10] Thus, a mixture of *cis*- and *trans*-1-lithio-2-methyl-2-vinylcyclopropane,[11] obtained from the metallation of the corresponding bromides, upon reaction with isobutyraldehyde and oxidation (pyridinium chlorochromate)[12] of the resulting alcohols provided a mixture of ketones **14** (R = Me, cis and trans). Treatment of this mixture with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) followed by quenching with trimethylsilyl chloride afforded the siloxydivinylcyclopropanes **15** (R = Me, cis and trans). Thermolysis (165–175 °C, 1.5 M benzene solution) of this mixture followed by desilylation (*n*-BuLi, THF, 25 °C, 5 h) of the resulting diene **16** (R = Me) provided karahanaenone (**17**, R = Me) in an overall yield of 54% based on isobutyraldehyde.

Studies on the preparation of more highly functionalized reagents and the application of these reagents in synthesis are in progress.

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(4) Compound **3a**: ir (neat) 1695 and 1635 cm^{-1}; NMR (CCl_4) δ 0.80–2.4 (complex m with br s at 1.71, 11 H) and 4.80–5.68 (m, 3 H).
(5) All new compounds reported were homogeneous by TLC or VPC and gave satisfactory ir and NMR spectra and exact mass or combustion analyses.
(6) Compound **3b**: ir (neat) 1695 and 1635 cm^{-1}; NMR (CCl_4) δ 0.80–2.60 (complex m with br s at 1.71, 11 H) and 4.80–5.50 (m, 3 H).
(7) Alternatively the divinylcyclopropanes may be isolated by distillation in which case the distillate is contaminated with varying amounts of the annelated product depending on the temperature used for the distillation. Pure samples of **3b** obtained by silica gel chromatography, upon standing at ambient temperature, slowly rearranged into compound **4**. In the other cases reported in Table I Isolation of the intermediate *cis*-divinylcyclopropanes can only be accomplished by low temperature chromatography owing to significant rearrangement at room temperature.
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(9) Compound **4**: bp 54–59 °C (0.15 mm); ir (neat) 1740 cm^{-1}; NMR (CCl_4) δ 1.09 (s, 3 H), 2.05–3.10 (complex m, 8 H), and 5.30–5.77 (m, 3 H).
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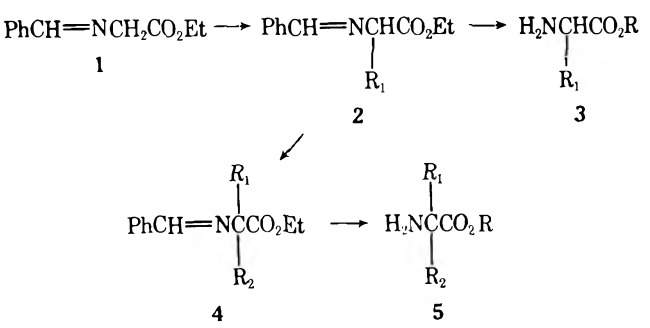
Alkylation and Michael Additions of Glycine Ethyl Ester. Use in α-Amino Acid Synthesis and as Acyl Carbanion Equivalent

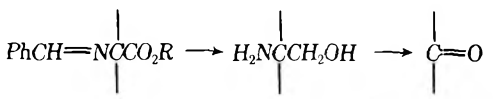
Summary: The benzylidene derivative of glycine ethyl ester can be used in mono- or sequential dialkylations thus leading to very simple syntheses of α-amino esters and acids; michael addition can also be effected readily, especially in protic solvents; the α-amino ester functionality can be transformed into a carbonyl (lithium aluminum hydride; periodate) and glycine ethyl ester is thus an acyl carbanion equivalent.

Sir: We would like to report that the readily available benzylidene derivatives of glycine esters can be alkylated in high yield under a variety of conditions. This obviously provides a particularly simple route to α-amino acids.[1]

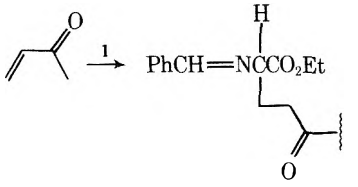
It is especially noteworthy that the relatively high acidity of **1** permits formation of the anion and its alkylation not only with strong bases like lithium diisopropylamide, but with weaker bases such as potassium *tert*-butoxide. Also noteworthy is the fact that these alkylations can be performed not only with the *tert*-butyl ester, but are very satisfactory with the simple ethyl ester, in spite of the "extreme instability" claimed for this substance.[2] Because an α-amino ester is a masked carbonyl group, the anion of a benzylidene glycine ester is also an acyl carbanion equivalent.[3] The latent carbonyl function may be unmasked, inter alia, via the sequence lithium



aluminum hydride reduction–periodate cleavage. Since either monoalkylation or sequential dialkylation of benzylidene glycine esters can be performed, either aldehydes or ketones can be synthesized by this method which is compatible with the presence of acid-sensitive functionality in the molecule.



An especially interesting feature of the anions derived from 1 and related esters, is the ease with which they undergo conjugate addition, e.g., with α,β-unsaturated ketones or esters. This is in contrast to the exclusive 1,2 addition found with the anion from the dialkyl derivatives of glycine esters[4] and is presumably a reflection of the more delocalized (softer)[5] character of the anion of the benzylidene derivative.



Alkylation. A. With Lithium Diisopropylamide (LDA). The lithium salt prepared by dropwise addition of 1.5 mmol of 1 to 1 equiv of LDA in 40 ml of dry tetrahydrofuran (THF) and 2.8 ml of hexamethyl phosphoramide at −78 °C was followed by 1 equiv of 1-iodooctane in THF. Warming to room temperature and stirring for another 4 h gave (workup with ice-cold aqueous ammonium chloride–ether) 2 (R = octyl), bp (k) 155 °C (0.07 mm),[6] in 90% yield. Alkylation with the secondary halide, isopropyl iodide, was effected in the same manner to give a 75% yield of 2 (R = isopropyl), bp (k) 126 °C (0.02 mm).

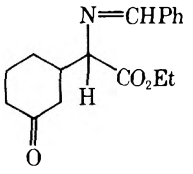
Functionality may also be present in the alkylating agent: ethyl bromoacetate and ethyl 6-bromohexanoate gave the corresponding monoalkylated products 2 (R_1 = $-CH_2CO_2Et$ and R_1 = $-(CH_2)_5CO_2Et$) in 82 and 62% yields, respectively.

B. With Potassium *tert*-Butoxide. Addition of 4 mmol of 1 in THF to a solution of 1 equiv of sublimed potassium *tert*-butoxide in 12 ml of THF, cooled to −78 °C, was followed by 1-iodooctane in THF. Stirring for 4 h after reaching room temperature and workup gave 2 (R_1 = octyl) in 78% yield.

Alkylation with 2 different alkyl groups could be performed without isolation of the monoalkyl product, e.g., by adding the solution from the first alkylation to another equivalent of LDA, followed by 1 equiv of the second halide. Sequential use of 1-iodobutane and 1-iodooctane thus gave an 81% yield of 4 (R_1 = butyl, R_2 = octyl), bp (k) 155 °C (0.05 mm).

The benzylidene derivatives of readily available α-amino acids can also be used in alkylation reactions. For instance, ethyl α-amino propionate (α-alanine ethyl ester) was alkylated as its benzylidene derivative 2 (R_1 = CH_3) with butyl bromide, by the general procedure A, to give 4 (R_1 = methyl, R_2 = butyl) in 77% yield.

Michael Additions of Benzylidene Glycine Esters. The benzylidene derivative of glycine ethyl ester underwent addition to 2-cyclohexenone in aprotic media, under the conditions described under Alkylation, but without hexamethylphosphoramide, to give the 1,4 adduct 6, in ~90% yield. It is especially noteworthy that the reaction can also be done easily in protic media, e.g., with 0.1 equiv of sodium ethoxide in dry ethanol at ~0 °C for 2 h to give 6, also in very high yield. The



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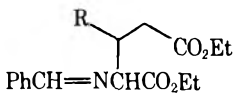

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corresponding crystalline *tert*-butyl ester, mp 100–101 °C, was similarly obtained. Alkoxide-catalyzed addition was also effected readily with ethyl acrylate, ethyl crotonate, and diethyl fumarate to give 7 (R = H), bp ~143 °C (0.04 mm), 7 (R = CH_3), bp 220 °C (0.2 mm), and 7 (R = CO_2Et), bp (k) 170 °C (0.04 mm), respectively, in 80–90% yields.

Hydrolysis to Amino Acids and Esters. Complete hydrolysis was effected by refluxing for 6 h with concentrated hydrochloric acid, followed by evaporation and addition of ethanol to the aqueous solution adjusted to pH 6. In this way, the (±) α-amino acids 3 (R = H, R_1 = octyl), mp 264–265 °C (reported[7] mp 264 °C), and 3 (R = H, R_1 = isopropyl) (valine), *N*-benzoyl derivative mp 129.5–130.5 °C (reported[8] mp 132.5 °C), were obtained in 90–100% yields. Partial hydrolysis to the α-amino esters could be effected with 5% hydrochloric acid for 2 h at room temperature. In this way, 3 (R = Et, R_1 = octyl), mp 69–71 °C from hexane (77% yield), 3 (R = Et; R_1 = $(CH_2)_2CO_2Et$), and 3 (R = Et; R_1 = $EtO_2CCHCH_2CO_2Et$) were similarly obtained in 70–90% yields and characterized by conversion to the known cyclic lactams.[9,10] In some cases, better results were obtained by passing the benzylidene ester through ~10 times its weight of acid-washed silica gel, followed by elution with ether after removal of benzaldehyde with pentane. The α-amino ester 5 (R = Et, R_1 = butyl, R_2 = octyl) was thus obtained in 82% yield.

Benzylidene Glycine Esters as Acyl Carbanion Equivalents. The aldehyde synthesis is illustrated by the synthesis of nonanal from octyl iodide. Reduction of 3 (R = ethyl, R_1 = octyl) with lithium aluminum hydride gave the related amino alcohol, 2-amino-1-decanol, mp 47.5–48 °C.[11] This was cleaved with a slight excess of periodic acid (room temperature overnight) to give, in essentially quantitative yield for the two steps, nonanal identical with an authentic sample.

The synthesis of ketones is shown by the conversion of 5 (R = ethyl, R_1 = butyl, R_2 = octyl) by the same procedure, in ~82% overall yield, into 5-tridecanone identical with an unambiguously synthesized sample.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health for their support of this work.

References and Notes

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(2) Prepared by treating 10.1 g of glycine ethyl ester hydrochloride in 150 ml of methylene chloride with 1 equiv of benzaldehyde in the presence of 20 ml of triethylamine and 6 g of anhydrous magnesium sulfate at room temperature, filtration, solvent removal (room temperature), water–ether partition washing (brine), drying, and removal of solvent. The substance thus obtained in 95% yield could be kept in the freezer for several months. See also O. Gerngross and A. Olcay, *Ber.*, **96**, 2550 (1963).
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(5) J. Durand, Nguyên Trong Anh, and J. Huet, *Tetrahedron Lett.*, 2397 (1974), and references cited therein.
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(12) On leave from the Université Pierre et Marie Curie, Paris.

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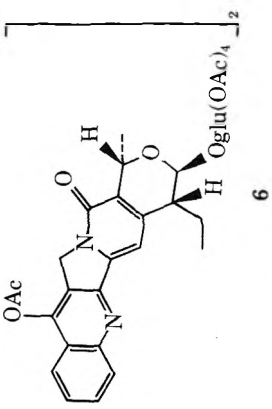
A Biomimetic Synthesis of the Camptothecin Chromophore

Summary: Novel heterocyclic alkaloids (**4** and **6**), potential synthetic precursors of 20(*S*)-camptothecin (**2**), are synthesized by 2,3-dichloro-5,6-dicyanobenzoquinone oxidation of tetraacetyl-18,19-dihydrovincoside (18,19-H_2-**1a**) and -isovincoside (18,19-H_2-**1c**) lactams and their corresponding pentaacetyl-18,19-dihydroquinolols (18,19-H_2-**3**).

Sir: We have been studying the chemistry[1] of the penultimate biosynthetic precursor of camptothecin (**2**), isovincoside lactam (**1c**), as a model system for the putative biochemical transformations that occur between **1c** and **2** in vivo.[2] Since D ring oxidation of **1c** to a pyridone may be one requisite of the biosynthetic pathway to **2**, we have examined the oxidation of 18,19-H_2-**1a** and -**1c** using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). Alternatively, D ring oxidation of isovincoside quinolol (**3c**) may be a key oxidative step preceding **2** in vivo, since presently we do not know the exact biochemical sequence of events between **1c** and **2**.[3] With both **1** and **3** oxidation with DDQ has been accomplished efficiently, which should enable a convenient synthesis of **2** and novel indole analogues of it, and which may be relevant to in vivo biosynthetic events.[4]

Oxidation of either 18,19-H_2-**1b** or -**1d** $(OAc)_4$ with DDQ (1 equiv or excess) in methanol (reflux, 5 min, N_2) or in a toluene–methanol mixture (25 °C, 5–10 min, N_2) gave a chromatographically resolvable mixture of **4a** [pale yellow solid: mp 145–150 °C dec; 41%; ir ν_{KBr} 3356 (NH), 1761 (OAc), 1667 (pyridone), and 1230 (C–O) cm^{-1}; uv λ_{max}^{MeOH} 386, 367, 296 (sh), 286 (sh), 273, 260, 252, and 213 nm; MS *m/e* 666.2437 ($M^{\cdot+} - CH_2O$, calcd for $C_{34}H_{38}N_2O_{12}$ 666.2424), 331.1026 [Glu$(OAc)_4^+$, calcd for $C_{14}H_{19}O_9$ 331.1024]; ^1H NMR (90 MHz) δ^{CDCl_3} 0.93 [t, 3 H, J = 7 Hz, C(18)], 1.89 [m, 2 H, C(19)], 2.00–2.07 (4 s, 12 H, 4 OAc), 2.58 [m, 1 H, C(20)], 2.95 [t, 2 H, J = 7 Hz, C(6)], 3.56 (s, 3 H, OCH_3), 4.35 [t, 2 H, J = 7 Hz, C(5)], 5.41 (d, 1 H, J = 3 Hz, C(21)], 5.70 [s, 1 H, C(17)], 6.32 (s, 1 H, C(14)], 7.08–7.54 (4 aromatic H), and 9.51 (br s, NH), glucosyl protons omitted] and **4b** [yellow needles (MeOH); mp 154–156.5°C; 26.5%; ir ν_{KBr} 3333 (NH), 1754 (OAc), 1658 (pyridone), and 1230 (C–O) cm^{-1}; uv λ_{max}^{EtOH} 418, 395 (sh), 324, 277, 257, 248 (sh), and 218 nm; MS *m/e*, 664.1897 ($M^{\cdot+} - CH_2O$, calcd for $C_{34}H_{36}N_2O_{12}$ 664.2258), 316.1153 [$M^{\cdot+}$ + 1 − CH_3O − (HO-(Glu$(OAc)_4$, calcd for $C_{20}H_{16}N_2O_2$ 316.1027], and 290.1419 (calcd for $C_{19}H_{18}N_2O$); ^1H NMR (90 MHz) δ^{CDCl_3} 1.02 [t, 3 H, J = 7 Hz, C(18)], 1.90 [m, 2 H, C(19)], 1.96–2.07 (4 s, 12 H, 4 OAc), 2.90 [m, 1 H, C(20)],



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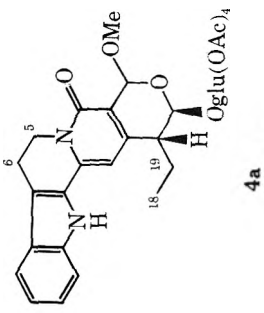
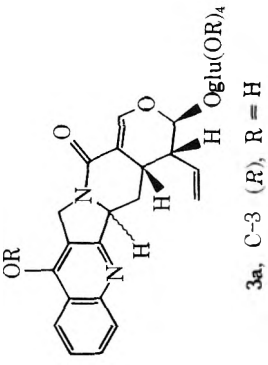
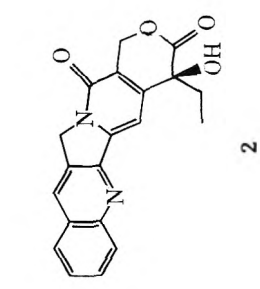


4a
b, $\Delta^{5,6}$



3a, C-3 (*R*), R = H
b, C-3 (*R*), R = Ac
c, C-3 (*S*), R = H
d, C-3 (*S*), R = Ac



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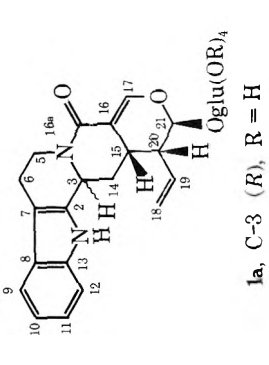


1a, C-3 (*R*), R = H
b, C-3 (*R*), R = Ac
c, C-3 (*S*), R = H
d, C-3 (*S*), R = Ac

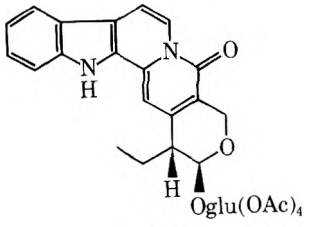
Table I. ^{13}C NMR Assignments[a]

Compd	Carbon resonances at 22.6 MHz[b]																	
	18	19	6	5	20	OMe	21	14	17	12	16	10	9	11	8	13	2	3	15	16a
4a	10.4	19.5	22.7	40.6	42.6	56.2	96.0	96.5	100.1	114.6	119.6	120.2	124.6	125.7	127.2	138.7	138.0	146.7	148.3	160.4
4b	11.1	21.1	111.9	108.8	43.8	56.3	96.1	96.1	98.1	110.6	118.6	120.5[c]	126.7	120.7[c]	129.9	132.9	139.8	144.3	146.5	156.6
6	9.4	20.8	123.9	48.8	42.0		98.5	99.4	89.7	130.8	120.1	122.3	127.9[d]	129.6[d]	121.3	150.8	154.0	145.1	149.4	158.5

[a] Determined in $CDCl_3$ relative to TMS as internal standard by consideration of the ^{13}C NMR assignments of 1b and 1d and 2,[7] SFOR proton decoupling, and low power proton decoupling.[8] [b] Glucosyl tetraacetate resonances omitted. [c] These two assignments may be reversed. [d] These two assignments could be interchanged.

3.66 (s, 3 H, OCH_3), 5.49 [d, 1 H, J = 3 Hz, C(21)], 5.94 [s, 1 H, C(17)], 6.76 (s, 1 H, C(14)], 6.81 [d, 1 H, J = 6 Hz, C(6)], 7.20–7.80 (4 aromatic H), 8.70 [d, 1 H, J = 6 Hz, C(5)], and 9.50 (br s, NH), glucosyl protons omitted}. The EI high resolution MS data for **4a** and **4b** are not so accurate as would be desirable; however, (1) the exact masses for the corresponding ions of 18,19-dehydro-**4a** and -**4b** agreed well with the calculated values,[5] and (2) when the oxidation was done in MeOD, ions at *m/e* 699, 696, and 666 were seen for one isolable product, which must correspond to [16-^{2}H]-15,16-H_2-**4a** (**5**).[6] The structures assigned to **4a** and **4b** were confirmed by ^{13}C NMR analysis (Table I) and **4a** was convertible quantitatively to **4b** by further DDQ oxidation (benzene, 25 °C, 5 min).

When the oxidation of 18,19-H_2-**1d** was done in benzene (reflux, N_2, 30 min), several blue fluorescent products were produced (TLC); the principal one (~25% yield) appeared to be **7** [uv (MeOH) identical with that of **4b**; ^{1}H NMR resonances characteristic for hydrogens at C(5), C(6), and C(18)–C(21); MS *m/e* 664 (M^+)]. Interestingly, when **7** was obtained (in low yield) from oxidation of 18,19-H_2-1d with DDQ



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in MeOD, it did not contain ^{2}H suggesting that an intramolecular hydrogen migration had occurred to generate the C(17) methylene.[6]

The analogous oxidation of **3b** or **3d** (benzene, reflux, 20 h) gave the interesting dimer, **6** {pale yellow needles from $CHCl_3$–CH_2Cl_2–MeOH, mp 160 °C dec; 73%; ir ν_{KBr} 1761 (acetate), 1667 (pyridone), and 1230 (C–O) cm^{-1}; uv λ_{max}^{THF} 385, 367, 335 (sh), 290, 253, and 245 nm; MS *m/e* 678 (½ dimer − CH_3CO), and 330.0986 [½ dimer − CH_3CO − (HO)glu(OAc)$_4$; calcd for $C_{20}H_{14}N_2O_3$ 330.1001]; ^{1}H NMR (270 MHz) δ^{CDCl_3} 0.95 [t, J = 7 Hz, 3 H, C(18)], 1.90 [m, 2 H, C(19)], 2.03–2.09 (8 s, 24 H, 8 OAc), 2.51 [s, 3 H, C(7) OAc], 2.91 [m, 1 H, C(20)], 5.18 [s, 2 H, C(5)], 5.89 [d, 1 H, C(21)], 6.45 [d, 1 H, C(17)], 7.24 [s, 1 H, C(14)], 7.60–8.15 (4 aromatic H), glucosyl protons omitted}. Anal. Calcd for $C_{72}H_{74}N_4O_{28}$·$CHCl_3$: C, 56.11; H, 4.84; N, 3.59. Found: C, 56.34; H, 4.80; N, 3.52. Although the foregoing data, except for the observation of eight distinct acetate methyl resonances, could be interpreted as evidence for a monomeric structure, the dimeric nature of **6** was confirmed by the following data. (1) A molecular weight analysis (vapor pressure osmometry) gave 1390 as the true molecular weight (calcd 1443). (2) The ^{13}C NMR signal of C(17) at δ 89.7 (Table I) appeared primarily as a doublet on SFOR proton decoupling with $^2J_{CH}$ fine structure indicative of an ABX spin system, which is evidence for the subunit, –*CO*(*H*)–(*H*)*OC*–.[9] No ^{13}C NMR signal corresponding to a C(17) methylene was present, and the ^{13}C NMR assignments of the aromatic carbons of **6** were nearly identical with those of **2**.[2] (3) The CD spectrum (*c* 0.056 mg/ml, dioxane) of **6** {$[\theta]_{450}$ 0, $[\theta]_{376}$ − 2.39 × 10^5, $[\theta]_{358}$ − 1.24 × 10^5, $[\theta]_{351}$ 0, $[\theta]_{345}$ + 5.60 × 10^4, $[\theta]_{331}$ + 7.14 × 10^5, and — $[\theta]_{255}$ 0}, when compared with that of the 21(*R*) 21-OMe acetal of **2**[10] which has only a very weak (−) cotton effect between 450 and 350 nm, is good evidence for the presence of a substituent at C(17) giving an *S* absolute stereochemistry.[11]

The relative ease and efficiency of the oxidation of **1** and **3**, which also occurs on standing in the air, may be significant in the biosynthesis of **2**. Nevertheless, the preparation of **6** from tryptamine and secologanin in 36% overall yield should enable a high-yielding synthesis of **2** as well as novel heterocyclic analogs of it.[12]

Acknowledgments. We are grateful to Marv Thompson (University of Connecticut) and Professor H. Schnoes (University of Wisconsin) for mass spectral analyses; to Jim Blackbourn and Professor W. A. Gibbons (University of Wisconsin) for NMR determinations; and to the NIH (CA 17127-02) for partial support of this research. Professor R. T. Brown and his co-workers kindly informed us of their results obtained independently at Manchester, which corroborate certain of the results described herein.

References and Notes

(1) For the preceding paper, see C. R. Hutchinson, G. J. O'Loughlin, R. T. Brown, and S. B. Fraser, *J. Chem. Soc., Chem. Commun.*, 928 (1975).
(2) C. R. Hutchinson, A. H. Heckendorf, P. E. Daddona, E. W. Hagaman, and E. Wenkert, *J. Am. Chem. Soc.*, **96**, 5609 (1974).
(3) Dr. A. H. Heckendorf (unpublished results) has demonstrated that neither **3a** or **3c** are incorporated into **2** at a time (parallel feeding experiments) when **1c** is incorporated. The validity of such negative results must be held questionable, until confirmed by appropriate positive incorporations.
(4) C. R. Hutchinson and A. H. Heckendorf, *J. Am. Chem. Soc.*, submitted for publication.
(5) 18,19-dehydro-**4a**: *m/e* 314.105 [$M^+ - H_2$ − (HO)glu(OAC)$_4$, calcd for $C_{20}H_{14}N_2O_2$ 314.108]. 18,19-dehydro-**4b**: *m/e* 312.089 [$M^+ - H_2$ − (HO)glu(OAC)$_4$; calcd for $C_{20}H_{12}N_2O_2$ 312.092].
(6) R. T. Brown, University of Manchester, England, personal communication, 1974.
(7) A. H. Heckendorf, K. C. Mattes, C. R. Hutchinson, E. W. Hagaman, and E. Wenkert, *J. Org. Chem.*, **41**, 2045 (1976).
(8) I. H. Sadler, *J. Chem. Soc., Chem. Commun.*, 809 (1973).
(9) K. D. Barrow, R. B. Jones, P. W. Pemberton, and L. Phillips, *J. Chem. Soc., Perkin Trans. 1*, 1406–1407 (1975).
(10) Prepared from **2** by (*i*) reduction with $NaBH_4$ in $CHCl_3$–MeOH then (*ii*) acetalization with $(MeO)_3CH$, H^+ in refluxing MeOH {mp 288–90 °C; CD (*c* 0.025 mg/ml, dioxane) $[\theta]_{450}$ 0, $[\theta]_{369}$ −1.09 × 10^4, $[\theta]_{331}$ − 2.9 × 10^3, $[\theta]_{323}$ 0, $[\theta]_{302}$ + 1.05 × 10^4, and $[\theta]_{265}$ 0}.
(11) (a) G. G. DeAngelis and W. C. Wildman, *Tetrahedron*, **25**, 5099 (1969); (b) G. Snatzke and P. C. Ho, *ibid.*, **27**, 3645 (1971).
(12) In view of the continued, successful use of **2** in cancer chemotherapy by the mainland Chinese (P. Potier, personal communication, 1976), additional studies of this drug need to be done.
(13) Career Development Awardee of the National Cancer Institute (CA 00253), 1976–1980.

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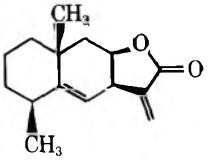
An Annelation Approach to the Eudesmane and Certain Elemane Sesquiterpenes

Summary. A potentially general route to eudesmane and certain elemane sesquiterpenes is demonstrated by synthesis of diene–lactone **9**.

Sir: We wish to describe what we consider to be a potentially general route to the eudesmane[1] and certain elemane sesquiterpenes, here illustrated by alanolactone (**1**) and ver-



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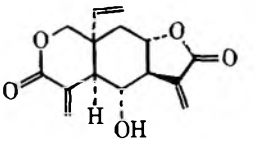
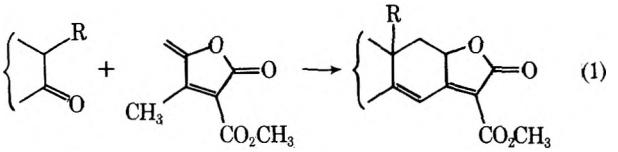


2

nomenin (**2**),[2] respectively. Our approach (eq 1), features the 1,6-annelation reagent α-carbomethoxy-β-methyl-γ-methylidene-$\Delta^{\alpha,\beta}$-butenolide (**3**), which incorporates the structural components of the γ-lactone (and furan) rings characteristic of these sesquiterpenes.[3]



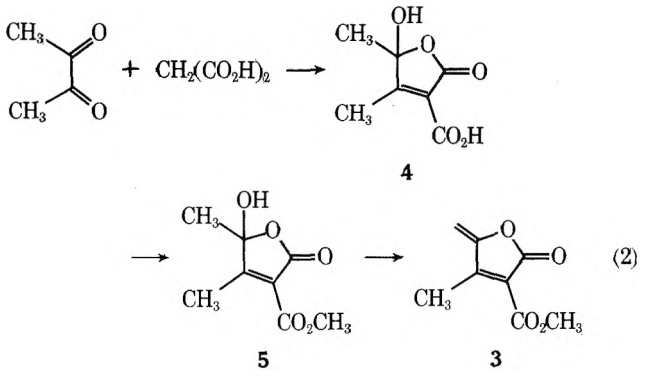
(1)

3

An exceedingly simple and high yield preparation of the required butenolide from equivalent amounts of biacetyl and malonic acid has been developed (80% overall yield, eq 2).[4] Although biacetyl has been reported to undergo multiple condensation with aldehydes in low to negligible yields using Knoevenagel conditions,[5] to our knowledge no successful re-

action between biacetyl and malonic acid derivatives has been reported; not unexpectedly, our initial attempts with standard Knoevenagel methodology were unsuccessful.

However, the desired condensation of biacetyl with malonic acid occurs with titanium tetrachloride[6] in pyridine–tetrahydrofuran (THF) solution to give the pseudo acid **4** in 89% isolated yield. Titration of **4** with diazomethane in ether gives the methyl ester pseudo acid **5** (mp 56 °C). Dehydration of **5**



(2)

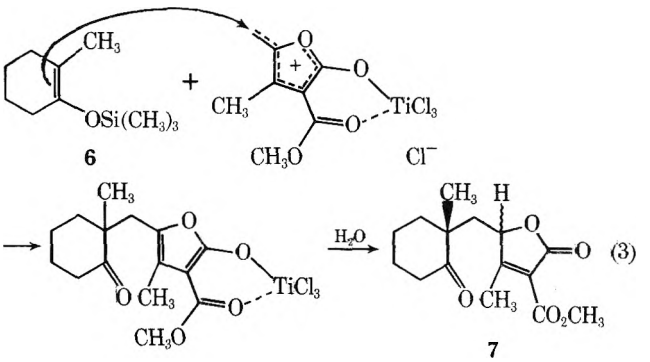
in a 1:10 solution by weight of phosphorus pentoxide in methanesulfonic acid[4,7] at 25 °C for 1.5 h gives butenolide **3** in 95% isolated yield.

Butenolide **3** may be isolated as an extremely unstable crystalline material (*m/e* 168.0426; calcd 168.0422), which does not exhibit a sharp melting point. The NMR spectrum of **3** in $CDCl_3$ displays singlets at δ 2.50 (3 protons) and 3.93 (3 protons) as well as doublets centered at 5.30 (1 proton, J = 4 Hz) and 5.43 ppm (1 proton, J = 4 Hz), and the ir spectrum is characterized by absorption at 5.58, 5.80, 6.08, and 6.17 μ ($CHCl_3$ solution).

The crystalline butenolide rapidly decomposes at room temperature to uncharacterized polymeric material; similar decomposition occurs in solution on treatment with aqueous sodium bicarbonate or amines. However, methylene chloride solutions of **3** may be refrigerated (−15 °C) for several hours with little decomposition. The extreme instability to a variety of bases suggests that **3** will not be useful in situations requiring classical Michael reaction conditions. In fact, even attempted addition of benzenethiol catalyzed by a trace of triethylamine resulted in instantaneous polymerization.[8]

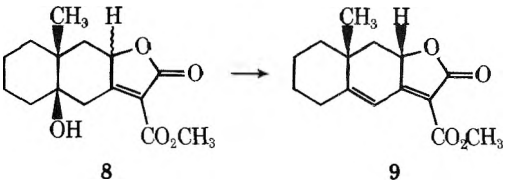
Recently Mukaiyama and coworkers have shown that silyl enol ethers react with α,β-unsaturated ketones in the presence of titanium tetrachloride to give 1,5-diketones.[9] We have found that butenolide **3** and silyl enol ethers undergo a remarkably rapid reaction with titanium tetrachloride to give 1,7-dicarbonyl compounds. The following procedure for the preparation of **7** is representative. To a solution of $TiCl_4$ (8.92 mmol, 0.98 ml) in dry CH_2Cl_2 (50 ml) at −78 °C is rapidly added a solution of **3** (8.92 mmol, 1.50 g) in CH_2Cl_2 (8 ml). After 2 min, a solution of silyl enol ether **6**[10] (8.92 mmol, 1.64 g) in CH_2Cl_2 (5 ml) is rapidly added. After the mixture is stirred for 4 min at −78 °C, aqueous K_2CO_3 (1.12 g in 50 ml of H_2O) is added to the deep blue solution to give **7**, isolated as a crystalline mixture of diastereomers in 50% yield (electron impact mass spectrum *m/e* 280). A possible mechanism for this transformation is presented in eq 3; a more definitive statement must await further study.

Completion of the desired annelation is accomplished by treatment of **7** with potassium carbonate in aqueous methanol to give a diastereomeric mixture of alcohols **8** in nearly quantitative yield.[11] Dehydration of **8** in a 1:10 solution by weight of phosphorus pentoxide in methanesulfonic acid at room temperature gives a mixture of diastereomeric dienes, which when treated with a trace of potassium carbonate in anhydrous methanol gives mainly one diastereomer **9** (95:5),



(3)

which may be obtained in pure form by crystallization from ether (mp 143–144 °C; *m/e* 262.1203; calcd 262. 1205; 60% yield from **7**).[12,13,14]



Thus, we have demonstrated that butenolide **3** should be a useful annelating reagent in the construction of linear tricyclic γ-lactones. Application of the methodology discussed here with respect to sesquiterpene total synthesis is currently being explored.

Acknowledgment. This work was supported by the National Institutes of Health (Grant CA 16624-02).

References and Notes

(1) For approaches to the eudesmane class of sesquiterpenes, see R. B. Miller and R. D. Nash, *J. Org. Chem.*, **38**, 4424 (1973), and references cited therein.
(2) Vernomenin and the related tumor inhibitor vernolepin have been the object of extensive synthetic effort. Recently, two total syntheses of these sesquiterpenes have been reported; see P. A. Grieco, M. Nishizawa, S. D. Burke, and N. Marinovic, *J. Am. Chem. Soc.*, **98**, 1612 (1976); S. Danishefsky, T. Kitahara, P. F. Schuda, and S. J. Etheredge, *ibid.*, **98**, 3028 (1976), and references cited therein, for related synthetic activity.
(3) For other 1,6-additions see S. Danishefsky, W. E. Hatch, M. Sax, E. Abola, and J. Pletcher, *J. Am. Chem. Soc.*, **95**, 2410 (1973), and references cited therein. Annelation of 1,3-dicarbonyl compounds with β-vinylbutenolide also has been reported; see F. Kido, T. Fujishita, K. Tsutsumi, and A. Yoshikoshi, *J. Chem. Soc., Chem. Commun.*, 337 (1975).
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(8) In contrast, treatment of the somewhat more stable α-carboethoxy-β-methyl-γ-ethylidene-$\Delta^{\alpha,\beta}$-butenolide with benzenethiol and a trace of triethylamine has been reported to result in nearly instantaneous 1,6-addition; see ref 4.
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(11) Suggested stereochemistry in **8** is proposed in accord with the base-catalyzed annelation of α-methylcyclohexanone with methyl vinyl ketone, which has been reported to give *cis*-10-methyl-2-decalon-9-ol; see H. B. Henbest and J. McEntee, *J. Chem. Soc.*, 4478 (1961), and J. A. Marshall and W. I. Fanta, *J. Org. Chem.*, **29**, 2501 (1964).
(12) Stereochemical assignment in **9** is based on a ^1H NMR double resonance experiment. Irradiation of the angular methyl resonance in the spectrum of **9** resulted in a 25% enhancement of the intensity of the resonance due to the methine hydrogen, indicating a cis relationship between these two substituents. We thank Iwao Miura of Columbia University for performing this valuable NOE experiment.
(13) Compounds **7**, **8**, and **9** give correct elemental analyses.
(14) **Note Added in Proof:** Diene **9** may be isolated in 80% overall yield from **7** more directly by treatment of **8** with acetic anhydride–sodium acetate at 105 °C for 6 h.

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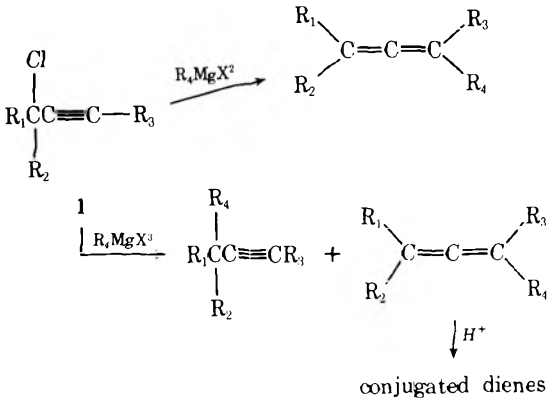
Reaction of Propargyl Halides with Grignard Reagents. Iron Trichloride Catalysis in Allene Formation[1]

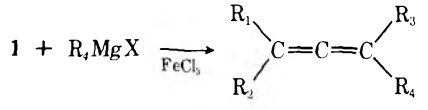
Summary: Ferric chloride catalyzes the highly selective formation of allenes in the reaction of propargyl chlorides with Grignard reagents; this procedure possesses many advantages for the preparation of allenes compared to those involving the reactions of lithium dialkylcuprates with proparyl and allenyl halides and acetates.

Sir: Several reports on the reactions of propargylic halides of general structure **1** with Grignard reagents have appeared describing contrasting results. In particular, Zakharova[2] describe the formation allenes as the major products, whereas Jacobs and Meyers[3a] report the formation of alkynes and conjugated dienes as major products, the latter later being shown to arise by facile acid-catalyzed isomerization.[3b] In a comprehensive study of the reactions of terminal and non-



terminal propargylic chlorides with organometallic reagents and transition metal catalysts, we have discovered a highly selective, iron catalyzed formation of allenes from the reactions of **1** with Grignard reagents.[4,5] The recent appearance of several articles describing the formation of allenes from propargylic and allenylic halides and acetates prompts us to report our preliminary results on the ferric chloride catalyzed formation of allenes from propargylic chlorides with Grignard reagents.

The reaction of both terminal (**1**, R_3 = H) and nonterminal (**1**, R_3 = CH_3) propargylic chlorides with primary and secondary Grignard reagents in the presence of 5×10^{-5} M ferric chloride results in the rapid formation of allenes in good yield[6] via proposed organoiron species similar to those proposed by



Koichi[7] in the coupling of vinyl halides with Grignard reagents.[5] In contrast, the reactions of terminal propargylic chlorides (**1**, R_3 = H) with primary Grignard reagents occur very slowly (24 h at 25 °C) to produce mixtures of terminal and nonterminal alkynes and allene via an allene carbene[8] intermediate,[9] while nonterminal propargylic halides react as reported by Jacobs and Meyers.[3] It is concluded that the difference between the results reported by Zakharova[2] and Jacobs and Meyers[3] must be due to presence of iron, or possibly some other transition metal, capable of catalyzing the allene forming process.

Table I. Yields of Allene Formation in Reactions of 1 with Grignard Reagents in the Presence of Iron

1	R_4MgX	% yield[a]
$R_1 = R_2 = CH_3$, R_3 = H	R_4 = *n*-Bu	80
$R_1 = CH_3$, $R_2 \approx R_3$ = H	R_4 = *n*-Bu	90
$R_1 = R_2 = R_3 \approx CH_3$	R_4 = *n*-Bu	87
$R_1 = R_2 = R_3 \approx CH_3$	$R_4 = CH_3$	40–43[b]
$R_1 = R_2 = R_3 \approx CH_3$	R_4 = *i*-Pr	88
$R_1, R_2 = -(CH_2)_5-$, $R_3 \approx$ H	$R_4 = CH_3$	84
$R_1, R_2 = -(CH_2)_5-$, $R_3 \approx CH_3$	$R_4 = CH_3$	45[b]
$R_1, R_2 = -(CH_2)_5-$, $R_3 \approx CH_3$	R_4 = *n*-Bu	70–80

[a] GLC yields. [b] Alkyne and allene are formed in a 1:1 mixture. Alkynes are not formed in the reactions of these substrates with *n*-butylmagnesium bromide.

The presently reported synthesis of allenes possesses several advantages over the recently reported syntheses of allenes using lithium dialkylcuprates[10] with propargyl and allenylic halides and acetates. In the reactions with the dialkylcuprates only one of the alkyl groups attached to the Cu is utilized, and the preparation of the reagent requires reacting the alkyllithium with cuprous halide. In contrast, our procedure uses the more easily and directly prepared Grignard reagent in 25–50% excess.[6]

A typical experimental procedure follows. To a solution of 0.0625–0.075 mol of 0.3 M Grignard reagent, to which a sufficient amount of ferric chloride in tetrahydrofuran is added to make the reaction mixture 5×10^{-5} M in ferric chloride, at 0 °C under a nitrogen atmosphere is slowly added 0.05 mol of the propargyl chloride in 15 ml of ether. After stirring at 0° for 15 min, the reaction mixture is hydrolyzed with water and worked up as normal. Table I lists the yields of allene formation in the reactions thus far studied.

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(3) (a) T. L. Jacobs and R. A. Meyers, *J. Am. Chem. Soc.*, **86**, 5244 (1964); (b) T. L. Jacobs and P. Prempree, *ibid.*, **89**; 6177 (1967).
(4) The magnesium used by Jacobs and Meyers[3] contained a stated impurity level of iron of ≤0.001% which corresponds to $\lesssim 4 \times 10^{-6}$ M iron in their experiments. The iron content of the magnesium used by Zakharova[2] was not indicated.
(5) A detailed description of this work and proposed mechanisms for product formation will be presented in subsequent full articles.
(6) Low yields (<5%) of dimeric products derived from the Grignard reagent and the propargylic chloride are also formed.[5]
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(8) For examples of nucleophilic attack on allenecarbene, see G. F. Hennion and J. F. Motier, *J. Org. Chem.*, **34**, 1319 (1969), and references cited therein.
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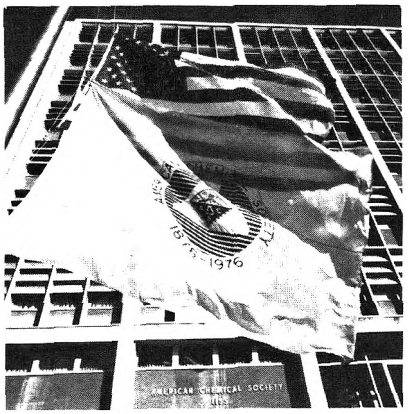

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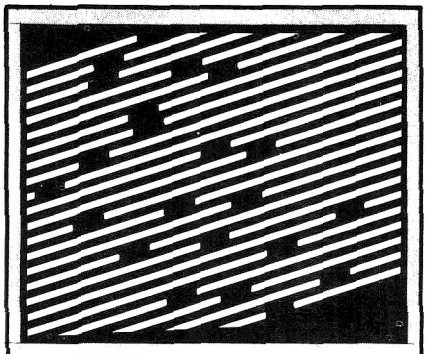

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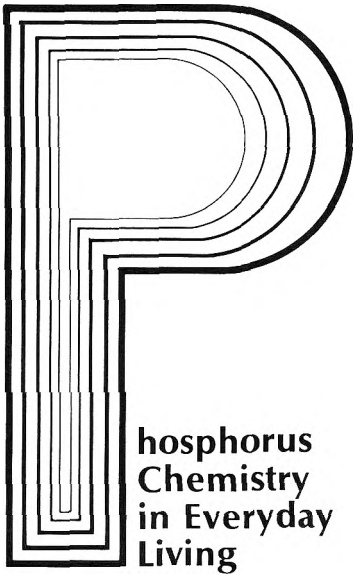

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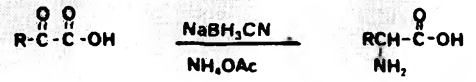
Sodium cyanoborohydride

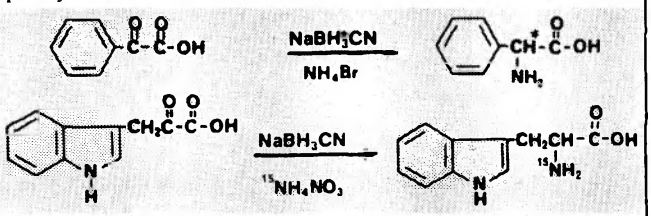
The properties and uses of the reducing agent **sodium cyanoborohydride** have been reviewed recently.[1] It is a milder, more selective reducing agent than sodium borohydride, and is stable in aqueous acid to pH 3. This has led to its use in a variety of new synthetic steps of importance to biochemists and natural product chemists.

Reductive Amination

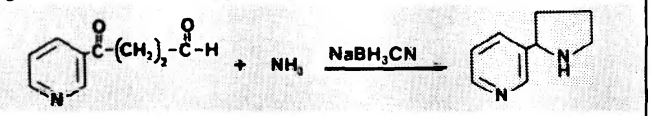
The reductive amination of substituted pyruvic acids provides a useful new synthesis of *dl*-α-amino acids.



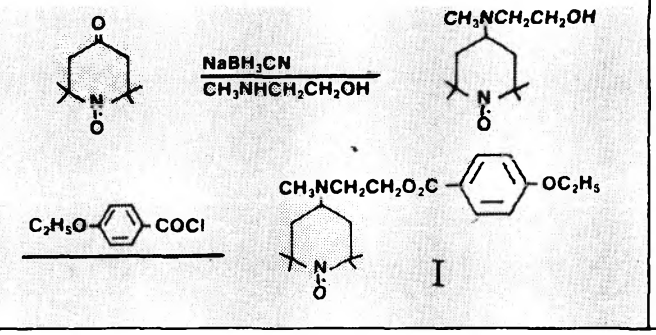
This reaction can also be used for the preparation of ^{2}H-, ^{3}H- or ^{15}N-labelled amino acids. The preparation of tritiated **sodium cyanoborohydride** and its use in the synthesis of phenylalanine-2-*t* have been described.[2]



Dicarbonyl compounds may be reductively aminated to give nitrogen heterocycles.[2,3]

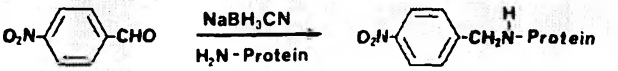


Reductive amination of 4-oxo-2,2,6,6-tetramethylpiperidinooxy free radical at pH 7-8 followed by treatment with 4-ethoxybenzoyl chloride gave the spin-labelled local anesthetic I.[4]



Sodium cyanoborodeuteride

The reductive amination of aldehydes enables the mild and selective alkylation of free amino groups in proteins.[5] Thus, wool, trypsin inhibitor, gluten and casein were reductively alkylated with *p*-nitrobenzaldehyde and **sodium cyanoborohydride** in lithium acetate buffer at pH 5.2, with yields of 64-90% of lysine modification.[5] The specificity of this procedure makes it more advantageous to nucleophilic alkylation in which other groups such as hydroxyl, mercapto and the imidazole moiety react.



Due to its poor stability in acidic medium, sodium borohydride proved less satisfactory in the above reaction.

Reduction

Yields of 69-100% were reportedly obtained in the reduction of saturated steroidal mono- and diketones, *e.g.*, estrone, pregnenolone acetate and androstane-3,17-dione with **sodium cyanoborohydride** at pH 1-3.[6]

The mild (aqueous, 3°C, pH 5) reduction of the imino linkage between 11-*cis*-retinal and the lipoprotein opsin has been reported.[7]

The stability of **sodium cyanoborohydride** at physiological pH has enabled the reduction of the enzyme UDP-galactose 4-epimerase-NAD^{+} complex.[8] Kinetic data for this reduction using sodium borohydride could not be obtained due to instability of the reagent at that pH.

Analogous reactions employing **sodium cyanoborodeuteride** yield the deuterated substrates.

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