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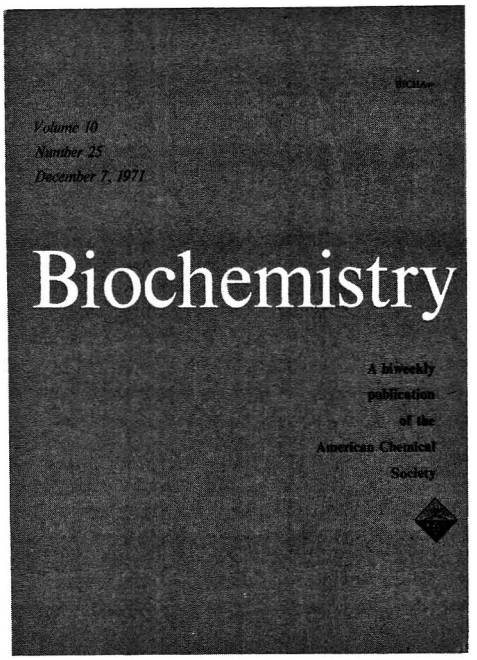

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Kinetic Evidence for Complex Formation in Alkene Bromination[1]

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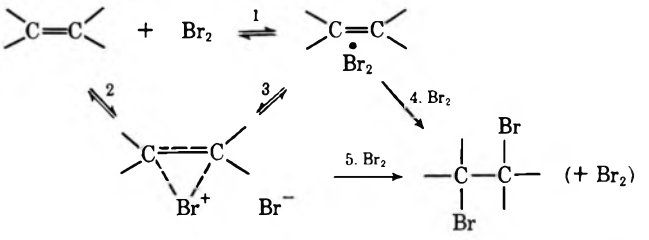
Received November 26, 1971

Kinetic and competitive bromination studies on simple alkenes in carbon tetrachloride support the hypothesis that complexation is an essential step in alkene bromination. The kinetic data were reproducible and showed that the reaction was first order in alkene and second order in bromine. These reaction rates were not retarded by a free-radical inhibitor. The observed reactivity order was (fastest to slowest) (*E*)-3-hexene:(*Z*)-3-hexene:(*E*)-4-octene. While the individual reaction rates were reproducible, the apparent third-order rate constants varied systematically with the alkene–bromine composition and were higher at higher bromine fractions. These results are consistent with predictions based on a kinetic model involving the formation of a bromine–alkene complex as the first step. Subsequent steps could involve the direct attack of a second bromine molecule on this complex or the formation of bromonium ions. Under competitive conditions, the relative reactivity of (*Z*)-3-hexene compared to (*E*)-4-octene was much greater than predicted from the kinetic studies. This enhanced reactivity is consistent with complex formation assuming that the (*Z*)-3-hexene complexes form more readily than the (*E*)-4-octene. This assumption is in agreement with the observed iodine–alkene complexation data.

The mechanism of alkene bromination has long been postulated to proceed *via* a bromonium ion intermediate.[2] This mechanism does account for the stereochemistry of addition[3] and the relative reactivity of various alkenes with bromine.[4,5] In addition, halonium ions have been observed experimentally in highly polar media.[6] Mechanisms involving charge-transfer complexes between the bromine and the alkene have also been advanced and these can account for much of the known experimental data.[7-13] However, there is little direct experimental data to support the hypothesis that the bromine–alkene complex plays an essential role in these mechanisms. While some evidence for the formation of such complexes has been claimed by spectroscopic[9,10] and flow techniques,[11] the complex need not lead directly to product, as outlined in Scheme I. Only routes 1–4 and 1–3–5 directly involve the complex in the reaction. Route 2–5 would circumvent this complex and in route 1–2–5 the complex is not an essential step in the reaction.

SCHEME I
GENERALIZED SUMMARY OF ALKENE BROMINATION REACTION MECHANISMS FOR SECOND- OR THIRD-ORDER REACTIONS



This investigation was conducted to see whether any kinetic evidence could be found that would support or reject a hypothesis that charge-transfer complexation is an essential step in alkene bromination. These kinetic studies were run in a nonpolar solvent, CCl_4, in order to minimize complex formation between bromine and the solvent, to restrict the complexation to the alkene and bromine, and to avoid mixed products due to solvent attack. Competitive bromination of pairs of alkenes were also studied in CCl_4 for direct comparison against these kinetic results.

Experimental Section

Materials.—Cyclohexene, (*E*)-3-hexene, (*Z*)-3-hexene, and (*E*)-4-octene were purchased from Chemical Samples Co.

(1) Presented in part at the Third Northeast Regional Meeting of the American Chemical Society, Buffalo, N. Y., Oct 11, 1971. Based, in part, on the Master's Thesis of G. D. F., Youngstown State University, June 1971.

(2) P. B. D. de la Mare and R. Boulton, "Electrophilic Addition to Unsaturated Systems," Elsevier, New York, N. Y., 1966.

(3) R. C. Fahey in "Topics in Stereochemistry," Vol. 3, E. L. Eliel and N. L. Allinger, Ed., Interscience, New York, N. Y., 1968, p 237.

(4) J. E. Dubois, F. Garnier, and H. Viellard, *Tetrahedron Lett.*, 1227 (1965), and references cited therein.

(5) S. V. Anantakrishnan and C. K. Ingold, *J. Chem. Soc.*, 984, 1396 (1935).

(6) J. M. Bollinger, J. M. Brinich, and G. A. Olah, *J. Amer. Chem. Soc.*, **92**, 4025 (1970), and references cited therein.

(7) D. V. Banthorpe, *Chem. Rev.*, **70**, 295 (1970).

(8) F. C. Fahey and H. J. Schneider, *J. Amer. Chem. Soc.*, **90**, 4429 (1968).

(9) R. E. Buckles and J. P. Yuk, *ibid.*, **75**, 5048 (1953).

(10) J. E. Dubois and F. Garnier, *Tetrahedron Lett.*, 3961 (1965); 3047 (1966); *Spectrochim. Acta, Part A*, **23**, 2279 (1967).

(11) G. Heublein and R. Rauscher, *Tetrahedron*, **25**, 3999 (1969).

(12) G. Heublein, *Z. Chem.*, **9**, 281 (1969).

(13) R. E. Buckles, J. L. Miller, and R. J. Thurmaier, *J. Org. Chem.*, **32**, 888 (1967), and references cited therein.

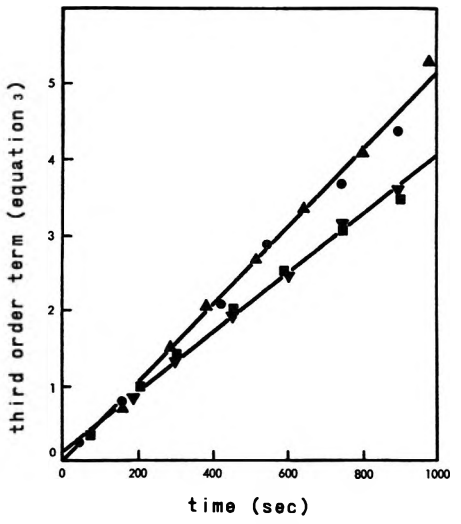


Figure 1.—Third-order plots for the bromination of (*Z*)-3-hexene (kinetic runs 9, ■, and 17, ▼) and of (*E*)-3-hexene (kinetic run 41; ●, uninhibited, and run 42, ▲, inhibited) in carbon tetrachloride.

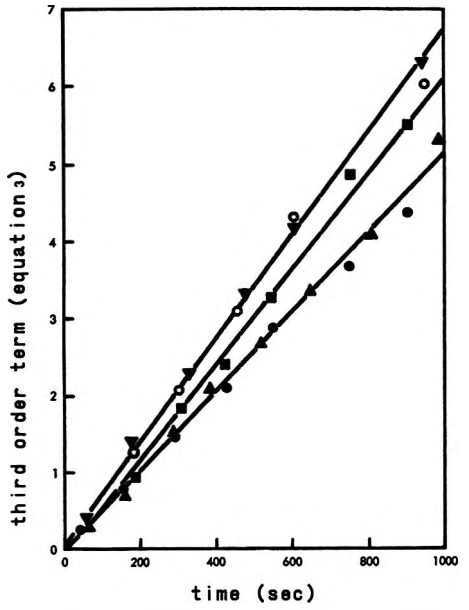


Figure 2.—Effect of the reaction concentration on the apparent third-order rate constants in the bromination of (*E*)-3-hexene in carbon tetrachloride: kinetic runs 38, ○; 39, ▼; 39, 40, ■; 41, ●; 42, ▲.

Since the purity of these alkenes was found to be at least 99% on several columns by glpc and the structures were confirmed by nmr and mass spectroscopy, they were used without further purification. Carbon tetrachloride was purified by a standard procedure[14] and distilled immediately prior to use. The purity was confirmed by glpc and uv. The purity of the 1-bromopentane (MC & B) was also shown to exceed 99% by glpc. The bromine and the iodine used were of the highest analytical reagent grade and were used without further purification.

Glassware.—Initially, all the glassware, including the quartz cells, used in the kinetic and competitive reaction studies were washed thoroughly, rinsed repeatedly with distilled water, dried, rinsed with purified CCl_4, and dried again. After each reaction, the glassware was cleaned by washing in purified CCl_4, drying, and storing in a desiccator. This procedure is essential in order to obtain reproducible kinetic data.

Kinetic Run Procedure.—The reaction rates for the alkene brominations were followed spectrophotometrically with a Cary 14 by determining the absorbance of the bromine solution at 415 mμ (ϵ_{max} 205.9 l./mol-cm) in 1-cm quartz cells. The diluted bromine and alkene solutions, in CCl_4, were allowed to equilibrate thermally in a darkened, controlled-temperature room and were then mixed in a reaction flask that was covered with aluminum foil to exclude light. Aliquots were removed periodically and the bromine absorbance was determined. The first reaction measurement was made within 2 min of mixing; then the reaction was followed for up to 20 min. Fresh aliquots were used for each absorbance determination in order to minimize possible light catalysis. The temperature was recorded during the reaction and had an average standard deviation of 0.14°. The concentrations and apparent third-order rate constants for these kinetic runs are summarized in Tables I [(*Z*)-3-hexene],

TABLE I

SUMMARY OF REACTION CONCENTRATIONS AND APPARENT THIRD-ORDER RATE CONSTANTS FOR THE BROMINATION OF (*Z*)-3-HEXENE AT 22.5°

Kinetic run	10^3 $(Br_2)_0$	10^3 $(Alkene)_0$	k, l.²/mol²-sec
1	8.88	9.07	45.7
2	8.88	7.04	48.8
3[a]	8.93	7.04	65.2
4	8.91	4.85	50.8
5	8.70	3.15	47.3
6	6.81	9.98	49.0
7	6.81	9.11	47.3
8	6.81	6.95	43.1
9	4.48	10.00	39.7
10	4.52	9.08	43.9
11	4.45	6.94	49.4
12	4.50	5.14	48.6
13	4.69	3.04	51.8
14	4.57	3.04	54.2
15	4.69	1.89	50.9
16	4.57	1.91	47.6
17	3.65	8.69	38.4
18	3.65	6.85	39.2
19	3.66	5.00	45.1
20	3.69	2.03	44.9

[a] Contains 2.7×10^{-3} *M* 2,6-di-*tert*-butyl-4-methylphenol.

II [(*E*)-3-hexene], and III [(*E*)-4-octene]. The reported rate constants were computed by the least squares method and the average per cent variance (100 standard deviation/k) was 2.17 for these experiments. Examples of individual kinetic runs are shown in Figures 1 and 2 and illustrate the reproducibility of the data.

In three experiments, noted in Tables I, II, and III, a substantial quantity of 2,6-di-*tert*-butyl-4-methylphenol was added to the reaction system to test whether a free radical reaction occurred along with (or instead of) the electrophilic addition of bromine. One of these reactions is also shown in Figure 1.

Recently, Pincock and Yates[15] showed that kinetic results for alkene bromination in acetic acid can be erroneous due to tribromide formation if this ion absorbs at the wavelength used for the monitoring. Although tribromide ion formation would not be expected in our solvent, we tested for the presence of an interfering species by making absorbance measurements at both 415 and 480 mμ (ε 123 l./mol-cm) for kinetic run 5, Table I. The same reaction rate was observed, indicating the absence of tribromide or any other interfering species.

Competitive Reactions.—The relative reactivity ratio of (*Z*)-3-hexene to (*E*)-4-octene was determined by the competitive reaction technique in CCl_4 at 25.0°. These reactions were run in flasks wrapped in aluminum foil to exclude light and the thermally equilibrated solutions were mixed in a darkened room to reduce the possiblility of a free radical reaction. All reaction solutions were 0.1 *M* in (*Z*)-3-hexene, (*E*)-4-octene, and 1-bromopentane (internal standard for glpc) and contained varying concentrations of bromine. The unreacted alkene concentrations were determined after 24 hr by glpc using a 5 ft × 0.125 in., 8% dinonyl phthalate on Anakrom ABS 90/100 mesh column at 70°

(14) J. A. Riddick and E. E. Toops, Jr., "Organic Solvents, Physical Properties and Methods of Purification," Interscience, New York, N. Y., 1955, pp 413–414.

(15) J. A. Pincock and K. Yates, *Can. J. Chem.*, **48**, 2944 (1970).

TABLE II

SUMMARY OF REACTION CONCENTRATIONS AND APPARENT THIRD-ORDER RATE CONSTANTS FOR THE BROMINATION OF (*E*)-3-HEXENE AT 22.5°

Kinetic run	10^3 $(Br_2)_0$	10^3 $(Alkene)_0$	k, l.²/mol²-sec
21	9.43	4.72	70.8
22	9.40	4.66	63.0
23	9.28	9.08	66.6
24	9.23	4.85	69.3
25	9.23	2.95	80.3
26	9.11	9.99	59.0
27	9.05	4.61	66.4
28	9.11	1.97	67.4
29	8.72	4.23	62.1
30	7.89	7.93	71.5
31	4.88	10.10	51.2
32	4.70	9.01	52.2
33	4.70	7.10	52.9
34	4.88	4.74	64.8
35	4.86	3.06	73.8
36	4.76	4.83	64.4
37	4.89	3.15	65.9
38	4.93	1.96	64.1
39	4.86	1.91	67.4
40	4.31	4.61	62.0
41	3.73	8.74	48.8
42[a]	3.68	8.70	53.0
43	3.73	6.87	53.7
44	2.55	4.34	52.5
45	2.04	4.28	46.0

[a] Contains 1.1×10^{-3} *M* 2,6-di-*tert*-butyl-4-methylphenol.

TABLE III

SUMMARY OF REACTION CONCENTRATIONS AND APPARENT THIRD-ORDER RATE CONSTANTS FOR THE BROMINATION OF (*E*)-4-OCTENE AT 22.5°

Kinetic run	10^3 $(Br_2)_0$	10^3 $(Alkene)_0$	k, l.²/mol²-sec
46	8.89	9.88	35.2
47	8.89	6.98	34.6
48[a]	8.93	7.01	44.8

[a] Contains 2.7×10^{-3} *M* 2,6-di-*tert*-butyl-4-methylphenol.

in a Carle Model 6500 gc. Each reacted solution and aliquots of the initial alkene solutions were analyzed five to six times by glpc and the moles of alkene present were computed using calibration curves for each alkene with 1-bromopentane, which served as an internal standard in the glpc studies. The ratio of the moles reacted of each alkene is shown in Figure 3 as a function of the initial bromine concentration. The relative reactivity can be obtained by extrapolating these ratios to zero bromine concentration, and the least squares regression curve is shown in Figure 3.

Iodine–Alkene Complexation.—The equilibrium constants were determined for the complexation of iodine with cyclohexene, (*Z*)-3-hexene, and (*E*)-4-octene in CCl_4 at 25° using a 1-cm quartz cell in the Cary 14 spectrophotometer. The equilibrium constants were computed from eq 1, where the initial iodine concen-

$$\frac{id}{A} = \frac{1}{K_N(\epsilon_c + \epsilon_i)N_0} + \frac{1}{\epsilon_c + \epsilon_i} \quad (1)$$

tration is i, d is the cell thickness, A is the absorbance of the complex at λ_{max} of the complex, K_N is the equilibrium constant in reciprocal mole fraction units, ϵ_c and ϵ_i are the molar absorptivities of complex and iodine at λ_{max} for the complex, and N_0 is the mole fraction of the alkene.[16]

The experimental procedure was similar to that of Traynham and Olechowski.[17] Stock solutions of iodine and alkene were covered with aluminum foil and equilibrated thermally. Aliquots were then mixed in flasks which were wrapped with aluminum foil to exclude light. The resulting reaction solutions ranged from 10^{-4} to 10^{-3} *M* iodine and the mole fraction of alkene ranged from 0.02 to 0.6. Samples were transferred to a 1-cm quartz cell within 2 min of mixing and the absorbance of the complex was measured at the wavelength shown in Table IV. Pure solvent was used as the reference. The absorbance of the complex did not change appreciably during the measurements, as was observed by other investigators.[18]

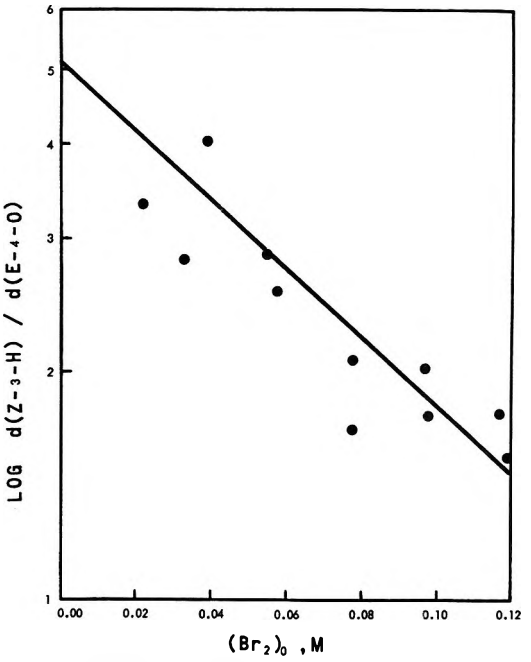


Figure 3.—Relative reactivities in the competitive bromination of (*Z*)-3-hexene [(*Z*)-3-H] and (*E*)-4-octene [(*E*)-4-0] at varying initial bromine concentrations. Initial alkene concentrations were 0.1 *M* in carbon tetrachloride.

TABLE IV

IODINE–ALKENE COMPLEXATION CONSTANTS IN CCl_4 AT 24.0°

Alkene	λ_{max}	10^{-4} ϵ_c, l./mol-cm	K_N[a]	K_C[b]
Cyclohexene	302	1.50	4.12	0.308
(*Z*)-3-Hexene	302	1.04	4.48	0.292
(*E*)-4-Octene	305	1.17	2.02	0.201

[a] Units are reciprocal mole fraction. [b] Units are l./mol.

A plot of id/A *vs.* $1/N_0$ gives a slope of $1/K_N(\epsilon_c + \epsilon_i)$ and an ordinate intercept of $1/(\epsilon_c + \epsilon_i)$, where $1/N_0$ is one. The molar absorptivity of iodine was determined independently to be 95 l./mol-cm at 295 m*M*. Table IV lists the equilibrium constants found in this study along with the observed values of λ_{max} and ϵ_c.

Results and Discussion

The existence of an alkene–bromine complex appears to be well established from the spectroscopic studies of Buckles and Yuk[9] and Dubois and Garnier.[10] Even in the absence of such spectroscopic data such a complex might be anticipated by analogy with iodine–alkene complexation.[17-19] As noted in Scheme I, the existence of a bromine–alkene complex does not necessarily mean that this complex is actually involved in the reaction pathway leading to the dibromide product. If such a complex were involved in the reaction mechanism it should be possible to detect its presence by kinetic and competitive studies, but other com-

(16) H. A. Benesi and J. H. Hildebrand, *J. Amer. Chem. Soc.*, **71**, 2703 (1949).

(17) J. G. Traynham and J. R. Olechowski, *ibid.*, **81**, 571 (1959).

(18) D. Long and R. W. Neuzil, *Anal. Chem.*, **27**, 1110 (1955).

(19) R. J. Cvetanovic, F. J. Duncan, W. E. Falconer, and W. A. Sunder, *J. Amer. Chem. Soc.*, **88**, 1602 (1966).

plexation reactions (*e.g.*, between bromine and solvent or between bromine and a polar group on the unsaturated compound) could confound these data. In our study we have circumvented this potential problem by using a nonpolar, noncomplexing solvent, CCl_4, and have restricted the unsaturated compound to simple internal alkenes. Although some kinetic measurements have been reported in nonpolar media,[13,20] these reactions often show extensive experimental scatter.[9,13] Part of this experimental problem could be due to trace impurities in the reaction media which would make the media more polar. Bromination reaction rates are known to increase with increasing solvent polarity.[4,13,20] In addition, alkene bromination rates are known to be sensitive to extraneous substances such as acids and halide ions.[2] A third source of experimental scattering would be the presence of a free-radical addition reaction along with the electrophilic bromination reaction.

In our studies, the solvent was purified immediately prior to each kinetic run in order to minimize the first two sources of error. Light was excluded from the reaction system to reduce the possibility of a free-radical reaction. The reactions were observed to follow third-order kinetics, as defined by eq 2 and 3,

$$\frac{dx}{dt} = k(a - x)(b - x)^2 \tag{2}$$

$$kt = \frac{1}{(a - b)}\left[\frac{x}{b(b - x)} + \frac{1}{(a - b)}\ln\left(\frac{a(b - x)}{b(a - x)}\right)\right] \tag{3}$$

where a and b are the initial concentrations of alkene and bromine, respectively, and x is the concentration of dibromide product at time t. Figure 1 illustrates the reproducibility of these third-order reactions for kinetic runs 9–17 and 41–42. Additional indications of reproducibility can be gained from Figure 2 and by comparing other replicate pairs of kinetic runs such as 13–14, 15–16, 21–22, and 38–39. The kinetic data are reproducible when the exact concentration conditions are duplicated. Figure 1 also shows that the reaction rate for (*E*)-3-hexene does not decrease in the presence of a free-radical inhibitor. This point is also illustrated for the other two alkenes in the kinetic pairs 2–3 [(*Z*)-3-hexene] and 47–48 [(*E*)-4-octene]. This data excludes a free-radical reaction as a significant part of this reaction. The increased rate of reaction in the presence of the inhibitor would be expected, since this phenol derivative would increase the polarity of the media.

Although replicate kinetic runs gave reproducible data, the observed rate constant varied widely when the concentrations of reactants changed. This effect can be seen in Figure 2 or in Tables I and II. The data shown in Figure 2 clearly show that the rate of reaction and their rate constants are reproducible for replicate brominations of (*E*)-3-hexene but that these rates change with the concentration. Under these circumstances, the observed specific rate constant for these reactions would be more appropriately termed an apparent third-order rate constant. As will be shown shortly, these apparent rate constants do not fluctuate in a random manner. It is entirely possible that many of the notations about experimental scatter in the literature arise from fluctuations of the apparent rate constant with the reactant concentrations. A similar phenomena was noted in the reaction of *cis*-stilbene with bromine in the presence of tetrabutylammonium tribromide in 1,2-dichloroethane.[13] In this case, the observed third-order rate constant increased with increasing concentration of the tetrabutylammonium tribromide, although no simple relationship was reported. If a bromine–alkene complex is directly involved in the reaction mechanism, the apparent third-order rate constant should fluctuate with the reactant concentrations.

Equations 4 and 5 show a simplified reaction se-

$$A + Br_2 \rightleftharpoons A \cdot Br_2 \tag{4}$$

$$A \cdot Br_2 + Br_2 \longrightarrow P + Br_2 \tag{5}$$

quence in which a bromine–alkene complex is an essential step. In these equations, A is the alkene and P is the dibromide product. Equation 4 shows the formation of the bromine–alkene complex as a reversible equilibrium reaction. The rate of formation of charge-transfer complexes is generally considered too fast to be measured by ordinary techniques.[21] This reaction can be defined by an equilibrium constant, K_4, and rate constants k_4, k_{-4} for the forward and reverse reactions, respectively. The reaction of the complex with a second bromine molecule in eq 5 leads irreversibly to product and would be defined by a rate constant k_5. This step would be rate determining and would result in third-order kinetics, as observed. Equation 5 may be a simplification of the actual sequence, which could involve bromonium ion formation, etc., but this is not essential at this point. The sequence shown by eq 4 and 5 can be treated mathematically by the steady state–equilibrium approximation.[22] The rate of reaction, from eq 5, can be expressed by eq 6,

$$\frac{dx}{dt} = k_5 c(b - x - c) \tag{6}$$

where a and b are the initial concentrations of alkene and bromine, respectively, x is the concentration of dibromide formed in time t, and c is the concentration of the complex. Using the steady-state assumption, the value of c can be defined by eq 7, which can be com-

$$c = \frac{K_4(a - x - c)(b - x - c)}{1 + \dfrac{k_5(b - x - c)}{k_{-4}}} \tag{7}$$

bined with eq 6 to produce the modified rate expression shown as eq 8. In order for the steady state–

$$\frac{dx}{dt} = \frac{k_5K_4(a - x - c)(b - x - c)^2}{1 + \dfrac{k_5(b - x - c)}{k_{-4}}} \tag{8}$$

equilibrium assumption to apply, k_5 must be much less than k_4 and k_{-4}. Since complexation is very fast while bromination proceeds at a readily measured rate, this condition appears to be satisfied in the present case. Under these conditions, eq 8 can be approximated by eq 9. The only difference between eq 9 and 2 is that

$$\frac{dx}{dt} = k_5K_4(a - x - c)(b - x - c)^2 \tag{9}$$

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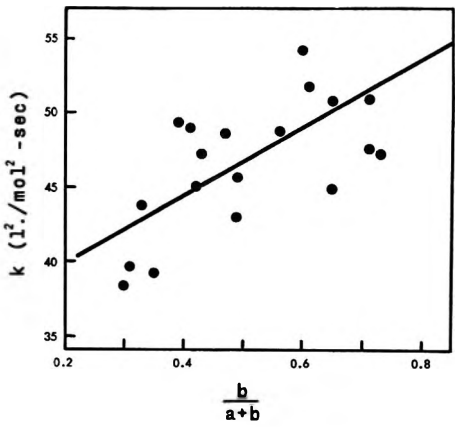

Figure 4.—Effect of the bromine reaction fraction on the apparent third-order rate constant for the bromination of (*Z*)-3-hexene in carbon tetrachloride.

the former contains the concentration of the complex. [Actually the terms $(a - x - c)$ and $(b - x - c)$ are the unreacted and uncomplexed alkene and bromine, respectively.]

Alternatively, eq 9 can be derived from an equilibrium approach. The equilibrium expression for eq 4 can be rearranged to give eq 10, which can be combined

$$c = K_4(a - x - c)(b - x - c) \tag{10}$$

with eq 6 to yield eq 9. Equation 9 contains two variable concentrations, x and c. Although c can be expressed in terms of K_4, a, b, and x, the resulting equation cannot be integrated readily and the value of c cannot be computed since K_4 is unknown. We can, nonetheless, evaluate the effect of the complex if we assume this concentration to be a constant and integrate eq 9 to get eq 11. This approximation would be valid for small changes in concentration.

$$k_5K_4t = \frac{1}{(a-b)}\left[\frac{x}{(b-c)(b-c-x)} + \frac{1}{(a-b)}\ln\left(\frac{(a-c)(b-c-x)}{(b-c)(a-c-x)}\right)\right] \tag{11}$$

The basic difference between eq 3 and 11 is that the latter contains the complex concentration and has a reaction constant that is a product of a rate constant and an equilibrium constant. The apparent third-order rate constants calculated from eq 3 can be considered as arising from eq 11 by ignoring the complex concentration. This neglect of the complex concentration introduces errors into the values of the reacting alkene and bromine and leads to incorrect values of the rate constant. The nature of this error is such that the apparent rate constant calculated from eq 3 will increase at b/a ratios greater than 1 and decrease when b/a is less than 1. This means that the apparent third-order rate constants should vary systematically with the concentrations of the reactants and that k should increase as the ratio of $b/(a + b)$ increases. Figures 4 and 5 show the observed apparent third-order rate constants for the reactions with (*Z*)-3-hexene and (*E*)-3-hexene, respectively, as a function of the fraction of bromine, $b/(a + b)$. In both cases, the observed third-order rate constant increases as the fraction of bromine increases, as predicted by the above analysis. The variation in the observed apparent third-order rate

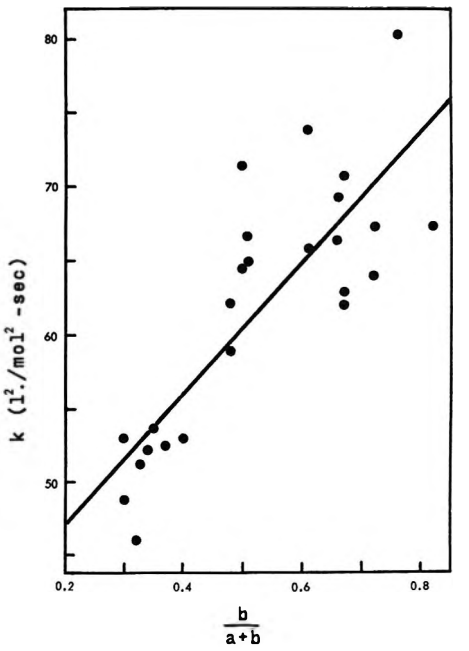

Figure 5.—Effect of the bromine reaction fraction on the apparent third-order rate constant for the bromination of (*E*)-3-hexene in carbon tetrachloride.

constant is consistent with a complex as an essential step in the reaction mechanism.

There are alternative explanations that do not involve a complex directly. If we consider the series of reactions shown by eq 4, 12, and 13, with k_{13} being

$$A + Br_2 \rightleftharpoons A\cdot Br_2 \tag{4}$$

$$A + Br_2 \longrightarrow ABr^+Br^- \tag{12}$$

$$ABr^+Br^- + Br_2 \longrightarrow P + Br_2 \tag{13}$$

the rate-determining step, we can derive eq 14. In

$$\frac{dx}{dt} = k_{12}k_{13}(a - x - c)(b - x - c)^2 \tag{14}$$

this sequence, which corresponds to route 1–2–5 in Scheme I, the complex is not directly involved in the reaction path but serves merely to change the concentrations of reactants which are available for reaction. While eq 14 is similar to eq 9, there are important differences. Equation 14 does not contain an equilibrium constant and this will be an important consideration in the competitive reaction data. In addition, eq 12 describes the formation of a bromonium ion. If k_{13} is rate determining, as is necessary for a third-order reaction, this step must be faster than eq 13 and the concentration of the bromonium ion should accumulate during the reaction. This condition appears unreasonable in the nonpolar media used in these studies. If we assume step 12 to be reversible, the resulting rate expression would be eq 15, which is essentially identical

$$\frac{dx}{dt} = K_{12}k_{13}(a - x - c - d)(b - x - c - d)^2 \tag{15}$$

with eq 9 except that the equilibrium constant describes the reversible formation of a bromonium ion whose concentration is denoted as d. The magnitude of the change in apparent rate constants shown in Figures 4 and 5 suggests that the concentration of the intermediate (complex and/or bromonium ion) is fairly large, and this requirement does not seem reasonable

for a bromonium ion in a nonpolar media. The direct evidence for bromonium ion formation has always been obtained in highly polar solvents.[6] If eq 12 is considered rate determining or if a steady-state assumption is applied to the bromonium ion concentration, second-order kinetics result. An equation similar to eq 14 can also be derived by the unlikely assumption of an intermolecular reaction between the alkene and two molecules of bromine. In general, the observed systematic variation of the apparent third-order rate constants with the reaction composition is inconsistent with mechanisms *not* involving a complex unless unusual assumptions are made.

Other reaction sequences are compatible with the data of Figures 4 and 5. Two such sequences are shown in eq 16, 17, and 18 and in eq 4, 19, and 18. In

$$2Br_2 \rightleftharpoons Br_4 \quad (16)$$

$$A + Br_4 \rightleftharpoons A\cdot Br_4 \quad (17)$$

$$A\cdot Br_4 \longrightarrow P + Br_2 \quad (18)$$

$$A + Br_2 \rightleftharpoons A\cdot Br_2 \quad (4)$$

$$A\cdot Br_2 + Br_2 \rightleftharpoons A\cdot Br_4 \quad (19)$$

$$A\cdot Br_4 \longrightarrow P + Br_2 \quad (18)$$

both cases, the rate-determining step, eq 18, involves the conversion of a 1:2 alkene–bromine complex to product and bromine. The rate expressions which can be derived from these sequences are similar to eq 9 and are consistent with the data of Figures 4 and 5. We have emphasized the sequence of eq 4 and 5 primarily because they are in accord with a 1:1 complex between the alkene and the bromine. There is no evidence to suggest a 1:2 (or higher) complex in these reactions and the 1:1 complex is analogous to the iodine–alkene complexes.[17-19] Even if these 1:2 complexes were assumed, the basic conclusions would be the same as in the treatment leading to eq 9.

The basic conclusion reached from eq 9 and 11 is that the systematic variation in the apparent third-order rate constant is due to complex formation between the alkene and the bromine. Other workers have reported systematic variation of apparent rate constants with concentration and have ascribed this effect to complexation between the reactants. Ross and Kuntz[23] have shown that the apparent second-order rate constant for the aromatic nucleophilic substitution reaction of 2,4-dinitrochlorobenzene with aniline decreases as the aniline concentration increases. Since their studies were made with excess aniline and constant 2,4-dinitrochlorobenzene concentrations, any possible effect of the 2,4-dinitrochlorobenzene concentration on the rate constant could not have been observed. Andrews and Keefer[24] showed that the apparent fourth-order rate constant for the reaction of iodine monochloride with mesitylene or pentamethylbenzene decreased as the concentration of the aromatic compound increased. Their studies used excess aromatic compound and approximately constant ICl concentrations so that effects due to the latter would not be observable. Variation of apparent rate constants with concentration has not been reported previously for alkene bromination, although it is possible that the experimental scatter reported by other workers is due to this effect.[13]

A second method of testing the intermediacy of a bromine–alkene complex involves the competitive reaction technique. In this technique, a pair of alkenes is treated with a limiting amount of bromine and the relative amounts of each alkene that react at infinite dilution of bromine should be equal to the ratio of the rate constants. For the bromination reactions, the relationship derived from eq 2 can be expressed by eq 19, where k and k' are the apparent rate

$$\frac{dA}{dD} = \frac{k}{k'} \quad (19)$$

constants for alkenes A and D, respectively, and the alkenes are present in an equimolar ratio. Equation 19 implicitly assumes that no complexation is involved in the reaction and relative reactivity ratio would be the same whether determined by a competitive technique or by a ratio of actual kinetic rate constants.

If a complex is directly involved in the reaction path, the situation becomes more complicated. The basic reactions can be described by eq 20–23. Under com-

$$A + Br_2 \rightleftharpoons A\cdot Br_2 \quad (20)$$

$$D + Br_2 \rightleftharpoons D\cdot Br_2 \quad (21)$$

$$A\cdot Br_2 + Br_2 \longrightarrow P_1 + Br_2 \quad (22)$$

$$D\cdot Br_2 + Br_2 \longrightarrow P_2 + Br_2 \quad (23)$$

petitive conditions, most of the bromine would be in the form of a complex due to the high alkene concentrations. The relative concentrations of each complex, $A\cdot Br_2$ and $D\cdot Br_2$, would not be the same as in independent kinetic reactions, since these competitive concentrations are established by the competing equilibria in eq 20 and 21. Assuming equimolar alkene concentrations, the bromine would be apportioned in these two complexes according to the ratio of the equilibrium constants as shown in eq 24. Under noncom-

$$\frac{(A\cdot Br_2)}{(D\cdot Br_2)} = \frac{K_{20}}{K_{21}} \quad (24)$$

peting conditions, the relative complex concentrations would be apportioned according to eq 25, where b is

$$\frac{(A\cdot Br_2)}{(D\cdot Br_2)} = \frac{K_{20}(b - c)}{K_{21}(b - e)} \quad (25)$$

the initial bromine concentration and c and e are the $A\cdot Br_2$ and $D\cdot Br_2$ concentrations, respectively.

If we assume that the complex is an essential step in the reaction, only complexed alkene can be converted to product. The limited amount of free bromine can either complex with excess free alkene or react with one of the two alkene–bromine complexes. Under these limiting conditions, the relative reactivity would approach the ratio of the equilibrium constants as defined in eq 26. The ratio in eq 19 and 26 should

$$\frac{dA}{dD} = \frac{K_{20}}{K_{21}} \quad (26)$$

normally be different if a complex is an essential step in the reaction mechanism.

Figure 3 shows the results of two series of competitive brominations of equimolar solutions of (*Z*)-3-hexene and (*E*)-4-octene. The extrapolated relative reac-

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(24) L. J. Andrews and R. M. Keefer, *ibid.*, **79**, 1412 (1957).

tivity is approximately 5.0 for the ratio d[(*Z*)-3-hexene]/d[(*E*)-4-octene]. This ratio corresponds to eq 26. The kinetic ratio corresponding to eq 19 can be obtained by dividing the rates of runs 1 and 2 (Table I) by the rates of runs 46 and 47 (Table III). The average kinetic relative reactivity is 1.35 ± 0.06. The competitive relative reactivity ratio is 3.7 times as great as the kinetic ratio. This is consistent with a complex as an essential step providing (*Z*)-3-hexene complexes more readily with bromine than does (*E*)-4-octene.

The use of the apparent third-order rate constants to estimate the relative reactivity of an alkene pair might appear questionable, since these apparent rate constants do vary with concentration. This method is reproducible, if the comparisons are made on the basis of equivalent concentrations. Thus the relative reactivity of (*E*)-3-hexene/(*Z*)-3-hexene is 1.34 ± 0.04 using six matched sets of data from Tables I and II. The pairs used are 23–1; 27–4; 37–13,14; 38,39–15,16; 41,42–17; and 43–18 and these sets comprise a wide concentration range. The individual k values vary but the ratios are constant.

No direct determinations of the equilibrium constants for bromine–alkene complexation are available. Normally, *Z* alkenes complex more extensively than *E* alkenes. The ratio of the equilibrium constants for *Z* alkene/*E* alkene has been reported as approximately 3–4 with $AgNO_3$[25–27] and 1.3–4.6 with I_2.[18,19,28] The magnitude of the $AgBF_4$–cyclohexene equilibrium constant has been reported to vary from 0.5 to 280 depending on the solvent.[29] In our studies we determined the iodine–alkene complexation constant for (*Z*)-3-hexene, (*E*)-4-octene, and cyclohexene in CCl_4 at 24° and these are summarized in Table IV. The equilibrium constant for cyclohexene in CCl_4 agrees reasonably well with values reported in nonpolar hydrocarbon solutions.[17,28] The *Z*/*E* complexation ratio was found to be in the range 1.5–2.2, showing that the (*Z*)-3-hexene does complex more extensively with iodine than does the (*E*)-4-octene. Since these data are on the same alkenes, in the same solvent, and use a related compound, iodine, as the complexing agent, it seems reasonable to expect the bromine–alkene complexation constant ratio to be similar. The greater electronegativity of bromine might increase the magnitude of the constants and could effect the ratio, but this change would not be expected to invert the ratio and make the *E* alkene complex more.

Our data and the literature data indicated that the *Z* alkene should complex more than the corresponding *E* alkene with bromine. An enhanced relative reactivity ratio in the competitive reaction studies is completely in accord with these complexation tendencies. This shift of the relative reactivity ratio in the direction corresponding to the complexation constant ratio is consistent with the hypothesis that a complex is an intermediate in the reaction path leading to product. If the complex is not directly involved, the individual rate expressions would be described by eq 14 and the relative reactivity ratio would contain only rate constants, as in eq 19. Since no equilibrium constant appears here, the two techniques for accessing relative reactivity should lead to the same ratio. Since they do not, we must reject the alternative hypothesis that the complex does not participate in the reaction as outlined in Scheme I, route 1–2–5. Our data do not distinguish between routes 1–4 and 1–3–5, since both would be affected by the complex in similar ways.

The presence of a bromine–alkene complex can account for the stereospecific trans addition of bromine to alkenes, especially in a third-order reaction. The stereochemistry of bromine addition has been studied by other workers and has been shown to depend on the structure of the alkene, the solvent, the concentration of the reactants, and the presence of halide ions.[8,13,30–32] Bromination becomes less stereospecific with increasing solvent polarity.[8,30,31] One possible explanation for this fact could be a shift of the reaction pathway from route 1–4 of Scheme I to route 1–3–5 due to solvent-assisted conversion of the complex to the bromonium ion. The resulting bromonium ion might be more readily susceptible to cis attack than the complex or might be in equilibrium with an open-chain bromocarbonium ion. This possible shift in reaction pathway could also account for the observed[2] shift from third-order to second-order kinetics with increasing solvent polarity. Similar decreases in reaction order with increasing solvent polarity have been observed in the electrophilic iodination of aromatic compounds by iodine monochloride.[24] The results of the present study are consistent with either route 1–4 or route 1–3–5 of Scheme I but there would appear to be no compelling reason to assume the existence of a bromonium ion in the bromination of alkenes in carbon tetrachloride.

Registry No.—(*Z*)-3-Hexene, 7642-09-3; (*E*)-3-hexene, 13269-52-8; (*E*)-4-octene, 14850-23-8; cyclohexene, 110-83-8.

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Bromination of 1,1-Diphenylethylenes. I. A Kinetic Study of Monosubstituted Derivatives in Methanol[1a]

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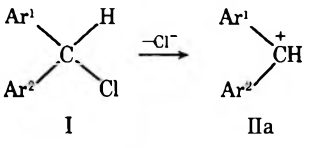
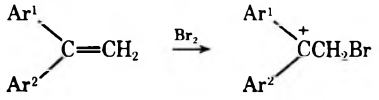
The kinetics of bromination of 11 meta- and para-substituted 1-aryl-1-phenylethylenes have been studied at 25° in methanol containing 0.2 *M* sodium bromide. The principal method used to study these rapid rates used an electrometric apparatus to maintain a constant low concentration of bromine in solution. Study of representative compounds showed that, under these conditions, molecular bromine was the only electrophilic species of importance. The rate constants for the meta-substituted compounds were correlated with $\rho = -3.57$ ($\log k_0 = 3.25$); this allowed the calculation of a coefficient for the transmission of resonance effects from the para position of the aryl ring of 0.84.

The reactivities of a large number of electrophilic side-chain reactions have been correlated using the unique set of σ^+ values of Brown and Okamoto.[2] However, Nishida[3] using more extensive data than previously available on the solvolysis of mono- and disubstituted benzhydryl chlorides (I) found that good correlations with σ^+ were only obtained when the substituent in one of the rings was varied, the other aryl ring being kept constant. Although simple additivity of substituent effects was observed in a limited number of cases,[3a,4,5] independent of their positions (meta or para) in either ring, in general it was concluded that the substituent effects were not additive (in the Hammett sense), not only when the two substituents were in different rings, but also when both were in the same ring.[3b]

This nonadditivity, where two substituents do not stabilize the transition state by the sum of the effects of the single substituents acting alone, appeared to be greatest when two substituents capable of electron donation by resonance were involved. However, whether this was due to saturation of resonance or the stereochemistry of the particular system chosen is not clear.



I IIa



III IIb

The kinetic method involved in solvolysis is limiting in that only a narrow range of reactivity can accurately be measured under a given set of conditions, the other rate values being estimated from data obtained in different conditions or at different temperatures. On the other hand, the bromination of 1,1-diphenylethylenes (III), which we have used to generate much the same kind of intermediate (IIb) as involved in the solvolysis reaction (IIa), is not subject to the same limitations. The reaction is very rapid when electron-donating substituents are present (up to 10^6 l. mol^{-1} sec^{-1}), but rate constants of this order are readily accessible when low concentrations of the reactants are used.[6] We report here a study of the bromination of a large number of monosubstituted 1,1-diarylethylenes. Using these results we can then hopefully define a model system showing "normal" behavior, thus leading to the separation of electronic and stereochemical factors which might contribute to nonadditivity.

Results and Discussion

Brominating Agent.—The bromination of 11 monosubstituted 1,1-diphenylethylenes has been studied at 25° in methanol containing 0.20 *M* sodium bromide (Table I). Under these conditions, little free bromine remains in solution, most of it being converted to tribromide ion, since the equilibrium constant (K) for the formation of tribromide ion is 177.[7] Bromination, however, may now conceivably take place by either of the brominating agents, molecular bromine or tribromide ion. It is important to know the relative amounts of bromination that occur by each of these two

TABLE I

RATE CONSTANTS[a] FOR THE BROMINATION OF SUBSTITUTED 1,1-DIPHENYLETHYLENES, $XC_6H_4C(=CH_2)C_6H_5$, IN METHANOL AT 25°

Registry no.	Substituent X	k_{obsd}, l. mol^{-1} sec^{-1}
4333-75-9	*p*-MeO	3.76×10^5
948-55-0	*p*-Me	1.56×10^4
4333-70-4	*m*-Me	3.28×10^3
530-48-3	H	1.67×10^3
34564-79-9	*m*-MeO	1.64×10^3
395-21-1	*p*-F	1.33×10^3
18218-20-7	*p*-Cl	4.73×10^2
4333-76-0	*p*-Br	3.61×10^2
29265-80-3	*m*-F	9.00×10
29265-81-4	*m*-Cl	7.30×10
29265-84-7	*m*-NO_2	7.00

[a] Listed in order of decreasing reactivity.

(1) (a) This paper may also be considered as part XXXI of the series "Olefinic Compounds Reactivity: Bromination." Part XXX: M. F. Ruasse and J. E. Dubois, *J. Org. Chem.*, **37**, 1770 (1972). (b) Chemistry Department, University College, Cork, Ireland. (c) 1851 Postdoctoral Fellow 1967–1968. (d) The Hebrew University of Jerusalem, Israel.

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species, since they would most likely have quite different responses to the variation of substituents in the aromatic rings.[8,9] Under these conditions, Bartlett and Tarbell[10] originally demonstrated that the overall expression (eq 1) is followed, where k_{obsd} is the observed

$$k_{obsd} = (\alpha + \beta[Br^-])/(1 + K[Br^-]) \quad (1)$$

second-order rate constant at a given bromide ion concentration, and α and β are constants. This has more recently been confirmed to a high degree of accuracy in the bromination of *trans*-stilbene over almost the complete range of possible variation of the $(1 + K[Br^-])$ term.[11]

Although other explanations are possible for the terms α and β, these are usually associated with k_{Br_2} and $Kk_{Br_3^-}$, respectively, where k_{Br_2} is the specific rate constant for the bromination of the substrate by molecular bromine, $k_{Br_3^-}$ by tribromide ion. The α term is the least controversial, since, when $[Br^-] = 0$, then $k_{obsd} = k_{Br_2}$. This value is obtained by the extrapolation of a plot of k_{obsd} $(1 + k[Br^-])$ *vs.* Br^- to zero bromide ion concentration, rather than by the determination of the rate constant in the absence of bromide ion. This latter condition would involve indefinite and complex rate expressions, since the quantity of bromide ion increases as the reaction proceeds and would complex with the unreacted bromine. The $k_{Br_3^-}$ term (contained in β) may represent rate-determining reaction with an electrophilic, polarized Br_3^- species or alternatively, being kinetically indistinguishable, successive reaction by Br_2 and Br^- (in whatever order) with the substrate.[12] Recent evidence suggests, however, that both mechanistic pathways may operate;[13] there is good evidence from the change in product with bromide ion concentration that in the bromination of acetylenes the $k_{Br_3^-}$ term represents Br^--assisted attack of Br_2.[14] This latter mechanism is to be favored in those cases where Br_3^- is apparently a better electrophile than Br_2.

Although no simple relation, applicable to all substrates, between the relative efficiency of the two apparent brominating agents ($k_{Br_2}/k_{Br_3^-} = Q$) and the structure of the substrate is available,[15] there is a general decrease in the ratio (*i.e.*, Q tends toward unity and in some cases is actually less than unity[16]) as the reactivity of the olefin within a given series decreases.[9] The least reactive olefin, *viz.*, 1-(*m*-nitrophenyl)-1-phenylethylene, was therefore chosen for study in detail since the intervention of Br_3^- (or $Br_2 + Br^-$) would be most critical here, together with two compounds of intermediate reactivity (see Table II). In each case the bromination by tribromide ion is relatively unimportant despite its large concentration in solution. The effect of bromide ion was studied under conditions where the ionic strength was not maintained constant by the presence of another salt, mainly since previous attempts to nullify specific salt effects in bromination reactions have not been successful,[17] different slopes (β) of k_{obsd} $(1 + K[Br^-])$ *vs.* $\{Br^-\}$ being obtained with different inert salts. In the absence of another salt the extrapolated k_{Br_2} value is at least free from salt effects.

TABLE II
EFFECT OF BROMIDE ION CONCENTRATION ON THE RATE OF BROMINATION OF SOME 1,1-DIARYLETHYLENES IN METHANOL AT 25°

A. 1-(*m*-Nitrophenyl)-1-phenylethylene

$[Br^-]$	k_{obsd}	
0.05	20.3	
0.10	13.2	$k_{Br_2} = 188$
0.15	9.90	
0.20	7.05	$k_{Br_3^-} = 2.67$
0.25	7.00	$Q = 70$

B. 1,1-Di-*p*-fluorophenylethylene

$[Br^-]$	$10^{-3}k_{obsd}$, l. mol^{-1} sec^{-1}	
0.05	3.27	
0.10	1.95	$k_{Br_2} = 3.06 \times 10^4$
0.15	1.61	$k_{Br_3^-} = 3.66 \times 10^2$
0.20	1.23	$Q = 85$
0.25	3.92	

C. 1-(*p*-Fluorophenyl)-1-phenylethylene

$[Br^-]$	$10^{-3}k_{odsd}$, l. mol^{-1} sec^{-1}	
0.05	3.92	
0.10	2.19	$k_{Br_2} = 3.16 \times 10^4$
0.15	1.63	$k_{Br_3^-} = 5.57 \times 10^2$
0.20	1.33	
0.25	1.30	$Q = 57$

The confidence limits of the utilization of k_{obsd} in place of the k_{Br_2} value in the estimation of linear free energy relationships have been mathematically calculated.[18] With Q greater than 50 (that is, $k_{Br_3^-}$ tending toward zero, as we have found), essentially the same results are obtained using either k_{obsd} or k_{Br_2}. This being the case, we have used the k_{obsd} value throughout in the evaluation of the rate data.[19] It is not possible to comment on the small variation of Q with structure, since values as large as this are very sensitive {as the slope of the plot of $(1 + K[Br^-])$ *vs.* Br^- plot nears zero} to the experimental error involved in measuring k_{obsd}; the final error in Q in the values quoted is therefore *ca.* ±20%, even though the k_{obsd} values are accurate to 3%.

Substituent Effects.—To establish unequivocally the true ρ value for the bromination of 1,1-diphenylethylenes, five meta-substituted compounds were chosen. Only the data for 1-(*m*-methoxyphenyl)-1-phenylethylene were omitted, since the σ_m^+ value for the *m*-MeO substituent has not been well established and may be variable in electrophilic reactions.[20] An excellent correlation was obtained with $\rho = -3.572$, $r = 0.999$, $s = 0.0047$, and $\log k_0 = 3.25$. It is clearly seen from

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(10) P. D. Bartlett and D. S. Tarbell, *ibid.*, **58**, 466 (1936).
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(14) J. A. Pincock and K. Yates, *Can. J. Chem.*, **48**, 3332 (1970); *J. Amer. Chem. Soc.*, **90**, 5643 (1968).
(15) E. Bienvenue-Goetz, D.Sc. Thesis, University of Paris, 1967; A. F. Hegarty and F. L. Scott, *J. Chem. Soc. B*, 1031 (1966).
(16) N. P. Kanyaev, *J. Gen. Chem. USSR*, **26**, 3037 (1956); **29**, 825 (1959).
(17) R. P. Bell and D. J. Rawlinson, *J. Chem. Soc.*, 63 (1961).
(18) J. E. Dubois and X. Q. Huynh, *Bull. Soc. Chim. Fr.*, 1436 (1968).
(19) In any event, the composite rate constant k_{obsd}, without the separation of the individual contributions due to Br_2 and Br_3^-, has been successfully used in many cases in studying the effect of molecular structure on reactivity; see, *e.g.*, J. E. Dubois and G. Mouvier, *Tetrahedron Lett.*, 1325 (1963); A. F. Hegarty and F. L. Scott, *J. Chem. Soc. B*, 672 (1966).
(20) Use of the σ_m^+ value of +0.048, given by Brown and Okamoto[2] for methoxy, does not disimprove the correlation.

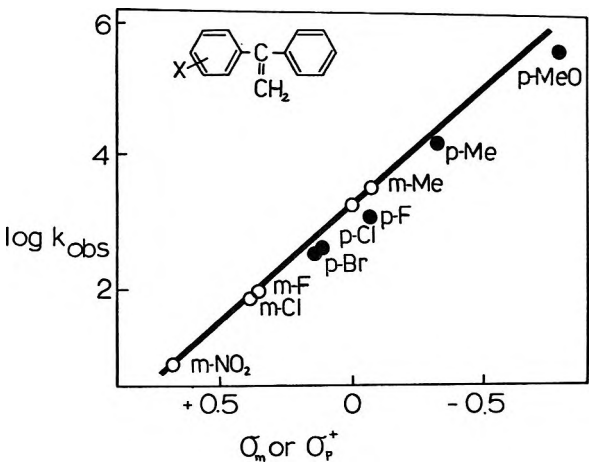

Figure 1.—Hammett plot of log k for the bromination of Ar(Ph)C = CH_2 *vs.* σ for meta-substituted compounds (O) and σ^+ for para-substituted compound (●), showing the overcorrelation for resonance involved in using the σ^+ values of Brown and Okamoto.[2]

Figure 1 that Brown and Okamoto's[2] σ^+ values place the kinetic data for all the para-substituted ethylenes *below* this line. This implies that resonance interactions between the substituents and the reaction center are somewhat less than in the defining reaction for σ^+. We have therefore applied the Yukawa–Tsuno equation[21] to the data for the para-substituted ethylenes in the form

$$\log k = -3.57(\sigma_0 + R\Delta\sigma^+) + 3.25$$

using the ρ value of −3.57 previously obtained from meta substituents. A least-squares treatment of the data for the five para-substituted 1,1-diphenylethylenes gave the resonance susceptibility constant, R = 0.84 (with r = 0.993, s = 0.019).[22] This value is remarkably close to that already reported (0.81) for substituent effects (by electron-donating substituents) on the pmr chemical shifts of the ethylenic proton of diphenylethylenes.[23]

The magnitude of R has been shown to decrease when the angle of rotation, ϕ, between the phenyl ring and the plane of the ethylenic bond is increased (resulting from decreased orbital overlap).[24] However, an estimate of the configuration of the molecule in the transition state can only be made if a reliable model is available for the situation when ϕ = 0°. If, as an approximation, it is assumed that this condition is met in the solvolysis of cumyl chlorides where R = 1.0,[2] then the R of 0.84 obtained in the present instance implies that ϕ = *ca.* 23° (if the susceptibility constant varies with $\cos^2\phi$).[25]

The ρ value obtained is lower than that reported by Nishida[3a] for the corresponding nonsubstituted benzhydryl chlorides (−4.22), also in methanol at 25°, or the bromination of meta- and para-substituted styrenes under the same conditions (−4.30).[26] However, the bromination of diphenylethylenes involves a transition state in which there is partial formation of a tertiary carbonium ion (IIb), whereas the solvolyses or the styrene bromination result in secondary carbonium ions (see IIa). The ρ value is found generally to decrease as the carbonium ion is successively primary, secondary, and tertiary; *e.g.*, the solvolysis of triphenylmethyl chloride in 40:60 ethanol–diethyl ether has a ρ of −2.34.[27] Moreover, any deviation from an open carbonium ion structure due to the participation of bromine as a neighboring group, although unlikely on the evidence for the bromination of styrenes,[9,28] would tend to reduce the sensitivity of the reaction to substituent effects. Also, any bromination by tribromide ion, although it has been shown to be an unimportant electrophilic species in the present study, would tend to reduce rather than increase the magnitude of the ρ value.[9,14]

Experimental Section

The 1,1-diarylethylenes were synthesized mainly using the Grignard reaction, either between the corresponding benzophenones and methylmagnesium iodide or between suitable acetophenones and arylmagnesium halides. The method is not applicable to the preparation of nitro-substituted 1,1-diarylethylenes. The Wittig reaction between nitrobenzophenone and triphenylphosphine–methylene gives generally very low yields, but Horner's modification of the Wittig reaction,[29] using triethyl phosphonoacetate, proved to be the only method of choice. The ester so obtained was not only hydrolyzed but also directly decarboxylated, when it was treated with a mixture of sulfuric and acetic acids.

Many of the compounds used in this study have been described previously.[30] The properties of the new substances are listed in Table III; in the following two representative syntheses are described.

TABLE III

ANALYTICAL AND PHYSICAL DATA FOR THE MONOSUBSTITUTED 1,1-DIPHENYLETHYLENES

$XC_6H_4C(=CH_2)C_6H_5$

X	Bp, °C (mm)	Yield, %
3-Me[a]	162 (18)	53
3-MeO[b]	185–187 (27)	64
3-NO_2[a]	146 (0.5)	25
3-F[a]	153–154 (22)	40
3-Cl[a]	185–187 (30)	31

[a] Satisfactory combustion analytical data (±0.3%) were provided for these compounds: Ed. [b] Calcd: C, 85.68; H, 6.71; MeO, 14.82. Found: C, 86.12; H, 6.70; MeO, 15.01.

1-(*m*-Tolyl)-1-phenylethylene.—To the solution prepared from *m*-bromotoluene (8.6 g) and magnesium (1.21 g) in anhydrous ether (50 ml), acetophenone (6.0 g) in ether (10 ml) was added slowly. The solution was refluxed for 2 hr and decomposed with 6 *N* hydrochloric acid (60 ml). Two distillations gave 5.6 g of the *ethylene*, bp 162° (18 mm). If dehydration did not occur spontaneously in the first distillation, a few crystals of iodine

(21) Y. Yukawa and Y. Tsuno, *J. Chem. Soc. Jap.*, **86**, 875 (1965); we use R rather than r for the resonance susceptibility constant, to avoid confusion with the correlation coefficient.

(22) This again demonstrates how many reactions appear to be well correlated by σ^+ values whereas in reality the use of the Yukawa–Tsuno equation on the basis of meta-substituted compounds to establish ρ gives an R value of 1.0 ± 0.3 [see, for example, P. R. Wells, *Chem. Rev.*, **63**, 171 (1963)]; part of the variation in σ is absorbed by the ρ value. In the present instance, use of σ^+ values for the ten substituted ethylenes gives a good fit (r = 0.996, s = 0.118), but the ρ value at −3.24 is significantly lower.

(23) Y. Yukawa, Y. Tsuno, and H. Yamada, *Mem. Inst. Sci. Ind. Res. Osaka Univ.*, **23**, 79 (1966).

(24) J. E. Dubois and A. F. Hegarty, *J. Chem. Soc. B*, 638 (1969).

(25) A. F. Hegarty and J. E. Dubois, *Tetrahedron Lett.*, 4839 (1968).

(26) J. E. Dubois and A. Schwarz, *ibid.*, 2167 (1964).

(27) A. C. Nixon and G. E. K. Branch, *J. Amer. Chem. Soc.*, **58**, 492 (1936).

(28) R. C. Fahey and H. J. Schneider, *ibid.*, **90**, 4429 (1968).

(29) L. Horner, H. Hoffmann, and H. G. Wippel, *Chem. Ber.*, **91**, 61 (1958); L. Horner, H. Hoffmann, H. G. Wippel, and G. Klahre, *ibid.*, **92**, 2499 (1959).

(30) F. Bergmann and J. Szmuszkovicz, *J. Amer. Chem. Soc.*, **70**, 2748 (1948); E. D. Bergmann and A. Bondi, *Chem. Ber.*, **63**, 1158 (1930); **64**, 1455 (1931).

were added and the product was redistilled. The distillate was then diluted with ether, washed free of any remaining iodine with an aqueous sodium thiosulfate solution, dried, and redistilled.

1-(*m*-Nitrophenyl)-1-phenylethylene.—In an atmosphere of dry nitrogen, triethyl phosphonoacetate (10 g) was added slowly to a suspension of sodium hydride (1.0 g) in 80 ml of dry dimethylformamide so that the temperature remained below 20°. After 1 hr at ambient temperature, *m*-nitrobenzophenone (10 g) was added and the mixture was heated, with vigorous stirring, at 120° for 4 hr. The mixture was then poured into 2 l. of cold water and the organic product was extracted with chloroform. The chloroform extract was washed (with water and then with concentrated sodium carbonate solution) and concentrated, and the residue was refluxed for 5 hr with glacial acetic acid (100 ml) and 10% sulfuric acid (80 ml). The solution was poured into 2 l. of cold water and the product was reextracted with chloroform. After washing (as before) and drying, distillation, bp 146° (0.5 mm), gave the olefin as a yellow solid. Several crystallizations from hexane gave 2.5 g of pure 1-(*m*-nitrophenyl)-1-phenylethylene, mp 82.5°.

In all cases the olefins were stored under nitrogen before use to minimize oxidation to the corresponding diaryl ketones. Even under these conditions, some oxidation took place; shortly before a kinetic run, the olefins were purified by vapor phase chromatography using an Aerograph Model 600-C chromatograph, with a 10-ft SE-30 column at 165–175°. All of the substrates thus obtained and used in the kinetic studies were greater than 99.5% pure. The purity of the substrates is, however, not critical when the concentrostat (see below) is used, provided that the impurities are brominated either much more rapidly or slowly than the olefin under study. Since the concentrostat employs a pseudo-constant concentration of bromine, the reaction is first order in (and therefore independent of the initial concentration of) the olefin.

Kinetic Measurements.—All kinetic experiments were at 25.0 ± 0.1° in methanol containing 0.20 *M* sodium bromide (unless otherwise stated). The methanol was reagent grade, treated as follows. Bromine (3–4 drops per liter) was added and, after standing overnight, the methanol was fractionated, the middle portion (50% of total) being retained. The distillate was similarly treated and redistilled; a final distillation from potassium carbonate removed small traces of hydrogen bromide formed. The methanol thus obtained contained less than 0.05% water (Karl–Fischer titration) and did not react significantly with bromine. No correction had to be made for the reaction of bromine with the solvent in a kinetic experiment if the time of reaction (10 half-lives) was less than 1 hr (and this was generally the case). The sodium bromide (Prolabo R. P. grade) was dried at 120° overnight before use.

Three electrometric methods were used to measure the rate constants which were all in the region $1–10^7$ l. mol^{-1} sec^{-1}. The actual method used for a given compound depended on its rate constant, since each method had an optimum region of operation, namely (1) potentiometric, $1–10^4$ l. mol^{-1} sec^{-1}; (2) concentrostat, $10^2–10^5$ l. mol^{-1} sec^{-1}; (3) amperometric, $>10^4$ l. mol^{-1} sec^{-1}. These barriers are not precise, however, and many compounds could be studied using more than one method. When this was possible, the various methods gave concordant results within the experimental errors listed. Each kinetic experiment was repeated a *minimum* of five times (and in many cases up to ten times), using various initial concentrations of olefin and bromine. The actual experimental errors, which varied with the magnitude of the rate constants, were as follows: $k > 10^4$, standard deviation 2%; $10^4 < k < 10^6$, 3%; $k > 10^6$, 4%. The calibration of the various apparatus was checked periodically using as standards compounds whose rate constants are well established, *e.g.*, cyclohexene,[31] k_2 = 790 l. mol^{-1} sec^{-1}, and allyl alcohol,[32] k_2 = 4.73 l. mol^{-1} sec^{-1}.

(1) The potentiometric method was essentially that used extensively by Bell and coworkers,[33] with the following modifications. A silver–silver chloride reference electrode (connected to the cell by a salt bridge containing a saturated methanolic solution of sodium bromide) was used with the platinum indicating electrode, and a Honeywell Model 1508 Visicorder was used to record the potential difference between these electrodes. Bromine was introduced coulometrically using Metrohm smooth platinum electrodes, the cathode being separated from the reaction solution by a fritted glass disk. The rate constant is given by

$$k_2 = -78.2\frac{dE/dt}{c}$$

where c is the olefin concentration and E is the potential difference (in volts) between the electrodes. The olefin was in at least a 20-fold excess, so that c is approximately constant; the rate constants were obtained directly from the resultant linear voltage–time plots. Changes in potential of 60 mV were followed representing >95% bromine reacted.

(2) The concentrostat, developed by Dubois and coworkers,[34] employs a constant concentration of bromine (*ca.* $10^{-5}–10^{-6}$ *M*) so that the reaction becomes pseudo-first-order in olefin. The cell, with a volume of 100 ml and thermostatted at 25°, contained three pairs of platinum electrodes, a thermometer, sample inlet, and stirrer. The bromine generation electrodes consisted of a platinum gauze (2 cm^2) anode in the reaction solution and a spiral platinum wire electrode (6 cm long, 1-mm diameter) in a second compartment containing a saturated methanolic solution of sodium bromide and separated from the reaction solution by a fritted glass disk. The bromine was generated using a pulse coulometer constructed in the laboratory (each pulse 0.12 sec duration) with currents varying from 3 to 60 mA depending on the constant bromine concentration required (which, in turn, was dependent on the rate constant being measured; higher bromine concentrations were used with slower reactions). To regulate the frequency of the pulses so that a constant bromine concentration was maintained as the bromine reacted with the olefin, two further electrodes (identical, each 2 cm long, 0.25 mm diameter) were dipped in the reaction solution. These were polarized by 0.6–4.6 V (the most sensitive position was sought) and connected to the concentrostat, which essentially regulated the bromine generation electrolysis current to maintain the current in the second circuit (and thus the bromine concentration) at the constant predetermined value. Typically, when 100 ml of the solvent had been introduced and the temperature had equilibrated, sufficient bromine was generated rapidly by electrolysis to give a final k_1 in the region 3×10^{-3} to 1.5×10^{-2} sec^{-1} (see below). The olefin was then added from a syringe, and the bromine was automatically maintained constant by the electrolysis current. After several such dry runs to optimize the reaction conditions and to condition the cell and electrodes to the substrate and reaction products, the total electrolysis time (*i.e.*, the number of current pulses multiplied by their duration) was plotted against the elapsed time using a printed read-out on a Hewlett-Packard Model H23563-A Digital Recorder.

Since the bromine concentration remains constant, a plot of the integrated electrolysis time (θ) against the elapsed time (t) gives the relation from which the rate constant with respect to the olefin is found.

$$k_1 = 2.303 \log \frac{(\theta_\infty - \theta_t)}{t}$$

θ_∞ is the calculated electrolysis time when $t = \infty$ which best fitted the relationship; this was invariably within 1% of the observed value. The observed second-order rate constant $k_2 = k_1/[Br_2^*]$. The constant bromine concentration ($Br_2^* = Br_2 + Br_3^-$) was determined amperometrically in the cell using the third pair of electrodes which were identical to the second pair but polarized by 0.2 V. An excess of arsenic acid solution was added, and the excess was determined titrimetrically against bromine. Finally the arsenic acid solution was standardized, also by titration against electrogenerated bromine.

(3) The coulometric apparatus, in which the limiting diffusion current of bromine at a rotating platinum electrode is measured as a function of time, has previously been described.[35] The exact initial bromine and olefin concentrations were determined by calibrating the recorder deflection each time using electrogenerated bromine; usually a bromine–olefin ratio of approximately 2:1 was used in these kinetic experiments.

Although no detailed product analysis was carried out in the present work, it has been shown that the bromination in benzene

(31) J. E. Dubois, M. Ropars, and P. Fresnet, *J. Chim. Phys.*, 856 (1965).
(32) J. E. Dubois and E. Goetz, *Tetrahedron Lett.*, 303 (1965).
(33) R. P. Bell and D. Dolmann, *J. Chem. Soc. B*, 500 (1968).
(34) J. E. Dubois and G. Mouvier, *C. R. Acad. Sci.*, **255**, 1104 (1962).
(35) J. E. Dubois, P. Alcais, and G. Barbier, *J. Electroanal. Chem.*, **8**, 359 (1964).

or chloroform solution, even of the most reactive substrates studied, *viz.*, 1-(*p*-methoxyphenyl)-1-phenylethylene, gives substitution products, *e.g.*, 1,1-diphenyl-2-bromoethylene from 1,1-diphenylethylene, in high yield.[36] In the methanolic solvent used in the present study, some solvent attack (giving methoxy bromo products) is conceivable, but would not alter the observed kinetics or conclusions. Dibromination, either at the 1 position or in the aromatic ring, was not apparent in any case (all the reactants followed clean second-order kinetics); moreover, the 2-bromo substituent (in the product) deactivated the olefin greatly to electrophilic attack; 2-bromo-1,1-diphenylethylene was brominated under the conditions used to study the kinetics approximately 10^5 times less rapidly than the parent 1,1-diphenylethylene.

(36) P. Peiffer and R. Wiziner, *Justus Liebigs Ann. Chem.*, **461**, 132 (1928).

Registry No.—1,1-Di-*p*-fluorophenylethylene, 6175-14-0.

Bromination of 1,1-Diphenylethylenes. II. Resonance Saturation and Geometrical Effects on the Reactivity of Multiply Substituted Derivatives[1,2]

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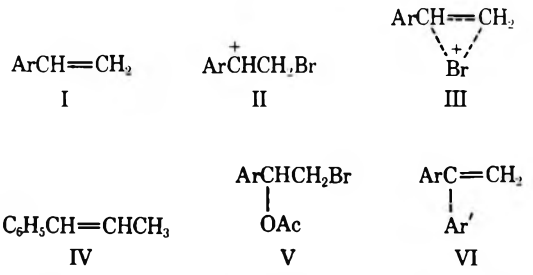
The substituent effects for multiple substitution on the kinetics of bromination of 1,1-diarylethylenes are not additive and exhibit apparent saturation of π-electron resonance stabilization. The majority of the rate constants can, however, be correlated, using a single reaction constant, by the linear parametric equation $\log k/k_0 = \rho(\sigma^+ + \sigma)$, with $\rho = -3.26$ and $\log k_0 = 3.169$. This is tantamount to postulating an unsymmetrical transition state in which one of the aryl rings remains planar and conjugated with the developing carbonium ion, the other ring (of necessity due to steric restriction) lying out of this plane. This equation is rigorously tested with 32 meta- and para-substituted diarylethylenes varying in reactivity by 7 powers of 10 (in MeOH at 25°). An alternative transition state in which both aryl rings are equally inclined to the plane of the carbonium ion proves less exact. A more detailed treatment, to include data for compounds which deviate from the above modified Hammett equation, requires that the presence of a substituent in one of the aryl rings also changes the ρ value for substituent variation in the second ring. The varying ρ's thus obtained for the bromination of 1-(substituted phenyl)-1-arylethylenes are -2.27 (substituent = *p*-MeO); -3.03 (*p*-Me); -3.57 (H); -3.67 (*p*-Br); -3.42 (*m*-Me); -3.69 (*m*-MeO); -4.08 (*m*-Cl); -4.65 (*m*-NO_2). The ρ values are proportional to the σ^+ of the substituent which is held constant. A similar multiple ρ treatment is found also to be applicable to data for the solvolysis of benzhydryl chlorides.

Recent studies by Yates and Rolston[4,5] and by Fahey and Schneider[6] have conclusively demonstrated that the electrophilic bromination of styrene derivatives I involves open benzylic-type carbonium ions II rather than cyclic bromonium ion intermediates III, as had previously been supposed. Thus bromination of *cis*- and *trans*-1-phenylpropene (IV) is nonstereoselective, both in carbon tetrachloride[6] and acetic acid solvents,[4] although the trans adduct is favored under most conditions. In acetic acid, solvent attack gives exclusively 1-acetoxy-2-bromo (V), rather than 1-bromo-2-acetoxy, products.[4] Kinetic evidence also



supports this conclusion, since the ρ values for the bromination of styrenes (-4.21 in acetic acid[5] and -4.30 in methanol)[7] are comparable to those commonly reported for α-phenylcarbonium ion formation (as in the solvolysis of carbinyl chlorides, where $\rho = -4.54$.)[8] Similar evidence has been presented[9] to support the existence of open-chain vinyl cationic species in the bromination of phenyl acetylenes.

This polarization of charge in the transition state would be expected to be far greater in the bromination of 1,1-diarylethylenes (VI). However, the rate enhancement reported on the introduction of one phenyl ring at the double bond (*i.e.*, styrene *vs.* ethylene) is greater (130-fold) than that for the introduction of the second aryl ring: 1,1-diphenylethylene is brominated only *ca.* 25 times more rapidly than styrene.[10] Clearly, part of this difference is due to the inability of the two aryl rings to be simultaneously coplanar with the double bond in VI (or in the carbonium ion formed from VI, which would have a similar sp^2 hybridized carbon center). However, the overall effect is an apparent "saturation" of resonance stabilization by the phenyl ring. Most reported cases of such saturation also involve substituents placed in such di- or triarylcarbonium ions[11-13] or carbanions.[14] It is of interest therefore to examine diphenylethylenes in which both aryl rings are substituted to discover whether simple geometric effects

(1) Part I: J. E. Dubois, A. F. Hegarty, and E. D. Bergmann, *J. Org. Chem.*, **37**, 2218 (1972).

(2) Some of the results presented here have been reported in communication form: E. D. Bergmann, J. E. Dubois, and A. F. Hegarty, *Chem. Commun.*, 1616 (1968); J. E. Dubois and W. V. Wright, *Tetrahedron Lett.*, 3101 (1967).

(3) (a) Chemistry Department, University College, Cork, Ireland; (b) 1851 Postdoctoral Fellow, 1967–1968; (c) NATO Postdoctoral Fellow, 1965–1966; (d) The Hebrew University of Jerusalem, Israel.

(4) J. H. Rolston and K. Yates, *J. Amer. Chem. Soc.*, **91**, 1469, 1477 (1969).

(5) J. H. Rolston and K. Yates, *ibid.*, **91**, 1483 (1969).

(6) R. C. Fahey and H. J. Schneider, *ibid.*, **90**, 4429 (1968).

(7) J. E. Dubois and A. Schwarz, *Tetrahedron Lett.*, 2167 (1964).

(8) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958).

(9) J. A. Pincock and K. Yates, *Can. J. Chem.*, **48**, 3332 (1970).

(10) J. E. Dubois and A. Schwarz, *C. R. Acad. Sci.*, **259**, 2227 (1964).

(11) J. Hine, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1962, p 100.

(12) S. Nishida, *J. Org. Chem.*, **32**, 2697 (1967).

(13) E. Berliner and M. Q. Malter, *ibid.*, **33**, 2595 (1968).

(14) L. D. McKeever and R. W. Taft, *J. Amer. Chem. Soc.*, **88**, 4544 (1966).

alone can account for the nonadditivity, using as a basis for normal behavior the ρ value previously obtained unequivocally for the monosubstituted compounds[1] under the same conditions.

Results and Discussion

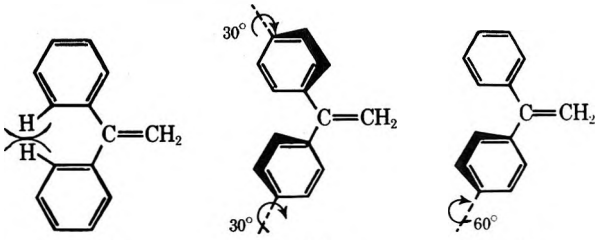
The rate constants for the bromination of disubstituted 1,1-diarylethylenes are summarized in Table I.

TABLE I
RATE CONSTANTS FOR THE BROMINATION OF SUBSTITUTED 1,1-DIARYLETHYLENES, $XC_6H_4C(=CH_2)C_6H_4Y$, IN METHANOL AT 25°

Compd	Substituents X	Substituents Y	k_{obsd}, l. mol^{-1} sec^{-1}
1	*p*-MeO	*p*-MeO	3.47×10^6
2	*p*-MeO	*p*-Me	9.73×10^5
3	*p*-MeO	*m*-Me	5.57×10^5
4	*p*-MeO	*p*-Br	1.07×10^5
5	*p*-Me	*p*-Me	9.83×10^4
6	*p*-MeO	*m*-Cl	5.03×10^4
7	*p*-MeO	*m*-Br	5.02×10^4
8	*p*-Me	*m*-Me	2.70×10^4
9	*p*-Me	*p*-F	9.93×10^3
10	*p*-MeO	*m*-NO_2	8.13×10^3
11	*p*-MeO	*p*-NO_2	7.31×10^3
12	*m*-Me	*m*-Me	6.45×10^3
13	*p*-Me	*p*-Br	4.12×10^3
14	*m*-MeO	*m*-MeO	1.31×10^3
15	*p*-F	*p*-F	1.23×10^3
16	*p*-Me	*m*-Br	8.80×10^2
17	*p*-Me	*m*-Cl	7.20×10^2
18	*m*-Me	*m*-F	1.83×10^2
19	*p*-Me	*m*-NO_2	1.28×10^2
20	*p*-Cl	*p*-Cl	1.27×10^2
21	*p*-Br	*p*-Br	1.03×10^2
22	*m*-MeO	*m*-Br	6.35×10
23	*m*-Cl	*m*-Cl	2.87

These constants, together with those previously reported for the monosubstituted 1-phenyl-1-arylethylenes,[1] cannot be correlated by plotting log k against any one one of the available sets of σ constants, *e.g.*, the σ^+ values proposed for electrophilic side chain reactions,[8] or ordinary Hammett σ values.[15] When either of these σ scales are used, curved plots with wide scatter of the points are obtained. Moreover, it is clear that the rate enhancements resulting from the combined effects of two substituents is not equal to the sum of the effects of the two substituents acting independently. This is most clearly seen by comparing the rate enhancements brought about by mono- and symmetrical disubstitution by the same substituent group (*e.g.*, *p*-MeO). This observed nonadditivity may be attributed to a combination of two major factors: (a) the geometry of the system and (b) the saturation of electronic effects in multiply substituted compounds.

A. Stereochemical Factors.—In 1,1-diphenylethylene (VII) it is not possible, because of interactions between the ortho hydrogens, for the two rings to lie in the plane of the double bond. From studies of the dipole moments of this system, Coates and Sutton[16] concluded that a conformation VIII in which the two rings were rotated out of the plane of the double bond by equal angle of *ca.* 30° (a propeller-like conformation) was the most stable; the repulsions between the ortho hydrogens in VII were then balanced by the decrease in resonance energy resulting from further rotation. More recently Casalone and Simonetta[17] have calculated an angle of rotation of *ca.* 35° for each ring from crystal studies on 1,1-di-(*p*-nitrophenyl)ethylene. These general concepts have since been confirmed by other studies using a variety of techniques on this[18,19] and other similar systems,[20] *e.g.*, benzophenones,[21] thiobenzophenones,[22] and tetraphenylcumulenes.[23] However, this structure VIII is not unequivocally established, since most of the data would also agree with a conformation (or a rapidly equilibrating mixture of conformations) in which one of the rings remains conjugated with the double bond, the other ring being twisted out of this plane by an angle greater than 60°



VII VIII IX

(IX). Because of the similarity of the two ultraviolet absorptions of 1,1-diphenylethylene (at 251 and 224 mμ in 95% ethanol) with those of styrene and simple unconjugated phenyl, Jones[24] proposed that 1,1-diphenylethylene had this perpendicular–planar structure IX. Further investigations using 2-methyl-substituted 1,1-diphenylethylenes, however, led Suzuki[25] to conclude that the rings were equally twisted, since the 2-methyl groups could be accommodated (and this is true only for VIII) without a large difference in the position of absorption. This conclusion in favor of VIII is also supported by the observation of a single nmr signal (even at −90°) for the two olefinic protons of 1,1-diphenylethylene;[19] on this basis, if we assume that the two rings are not equivalent, then interconversion between them must be rapid.

The energy difference between the two conformations (estimated assuming that the fractional reduction in resonance interaction due to the rotation of a phenyl ring out of coplanarity by an angle ϕ is, to a first approximation, related to $\cos^2 \phi$)[26] is not very great in the initial diphenylethylene. However, it may be critical in the transition state of the bromination reaction where the greater requirements of the stabiliza-

(15) D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).
(16) G. E. Coates and L. E. Sutton, *J. Chem. Soc.*, 567 (1942).
(17) G. Casalone and M. Simonetta, *J. Chem. Soc. B*, 1181 (1971).
(18) M. Simonetta and S. Carra, *Tetrahedron, Suppl.* **2**, **19**, 467 (1963).
(19) R. van der Linde, O. Korver, P. K. Korver, P. J. van der Haak, J. U. Veenland, and T. J. de Boer, *Spectrochim. Acta*, **21**, 1893 (1965); M. Rabinovitz, I. Agranat, and E. Bergmann, *Israel J. Chem.*, **7**, 795 (1969).
(20) I. I. Schuster, A. K. Colter, and R. J. Kurland, *J. Amer. Chem. Soc.*, **90**, 4679 (1968).
(21) J. Barassin, G. Queguiner, and H. Lumbroso, *Bull. Soc. Chim. Fr.*, 4707 (1967).
(22) O. Korver, J. U. Veenland, and T. J. de Boer, *Recl. Trav. Chim. Pays-Bas*, **81**, 103 (1962).
(23) H. Fischer and W. D. Hell, *Angew. Chem., Int. Ed. Engl.*, **6**, 954 (1967).
(24) R. N. Jones, *J. Amer. Chem. Soc.*, **65**, 1818 (1943); O. Korver, J. U. Veenland, and T. H. de Boer, *Recl. Trav. Chim. Pays-Bas*, **84**, 806 (1965).
(25) H. Suzuki, *Bull. Chem. Soc. Jap.*, **33**, 619 (1960).
(26) B. M. Wepster in W. Klyne and P. B. D. de la Mare, "Progress in Stereochemistry," Vol. 2, Butterworths, London, 1958, pp 102, 122.

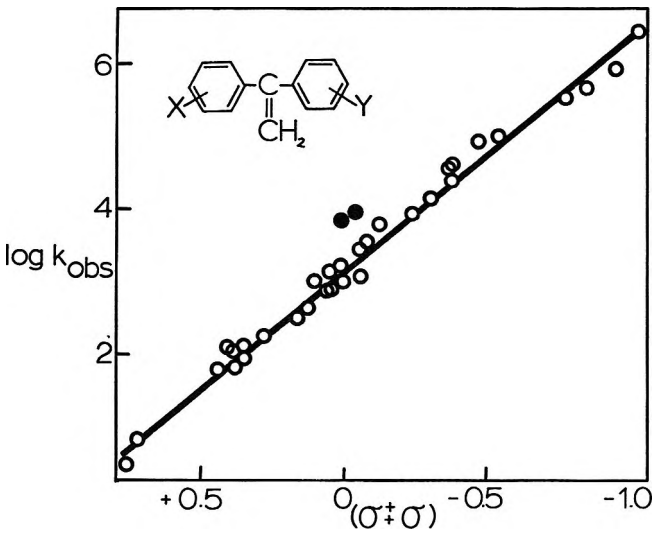


Figure 1.—Plot of log k for the bromination of 1,1-diarylethylenes in MeOH at 25° *vs.* $(\sigma^+ + \sigma)$, assuming a perpendicular–planar structure (IX) for the transition state. The σ^+ value is applied to all monosubstituted compounds (data from ref 1), and in disubstituted compound to the substituent with the largest $\Delta\sigma^+$ value. The two points (●) refer to data for 1-(*p*-methoxyphenyl)-1-(*m*- and *p*-nitrophenyl)ethylene (see text).

tion of a carbonium ion are involved, since it has been demonstrated[27] that, while inductive effects of substituents are transmitted with about equal effect regardless of the angle of twist ϕ, resonance effects are critically dependent on this angle, reaching a maximal value when the π orbitals of the phenyl ring and the vacant p orbital of the carbonium ion can best overlap.

Two simple approaches, 1 and 2, have been used to examine how closely the transition states of the bromination reactions can be related to the prependicular–planar (IX) and equally rotated (VIII) structures.

(1) The ratios log k_{MeO}/k_H and log $k_{(MeO)_2}$/log k_{MeO} are 2.35 and 0.97, respectively, and are approximately proportional to the σ^+ and σ values of the MeO group. This suggested an approach in which the kinetic data were correlated by assigning a σ^+ value to the substituent in all monosubstituted compounds and a σ value to the second substituent in a disubstituted compound. This assumes that the substituted ring in the transition state has a sufficiently important resonance interaction with the charged center that it aligns to permit optimal orbital overlap. The other ring, therefore, because of steric interactions, remains out of the plane sufficiently (at an angle >60°) so that there is essentially no resonance interaction between substituents in this ring and the reaction center. Application of this simple treatment, *viz.*, log $k = \rho(\sigma^+ + \sigma)$ + log k_0, gives an excellent relationship with $\rho = -3.26$, $r = 0.995$, $s = 0.596$, and log $k_0 = 3.169$.[28] Kinetic data for 32 ethylenes was used in this correlation (see Table I and Table I of ref 1); two disubstituted compounds in which both strong electron-donating and attracting groups were present, *viz.*, 1-(*p*-methoxyphenyl)-1-(*m*- and *p*-nitrophenyl)ethylenes, were omitted, but there were no other serious deviations from this equation (see Figure 1).

(27) A. F. Hegarty and J. E. Dubois, *Tetrahedron Lett.*, 4839 (1968).

(28) The symbols used throughout the r, correlation coefficient; s, standard deviation; and k_0, calculated rate constant when $\sigma = 0$ (see, *e.g.*, C. A. Bennett and N. L. Franklin, "Statistical Analysis in Chemistry and Chemical Industry," Wiley, New York, N. Y., 1954, p 245).

Significantly, when there was a choice in unsymmetrically disubstituted compounds as to which ring is to remain planar, a better fit is invariably obtained by applying the σ^+ value (and by implication the planar ring) to the strongest resonance-donating substituent (as measured by the magnitude of the difference $\sigma^+ - \sigma$). This is clearly seen by comparing the calculated and observed rate constants for the two arrangements which are listed in Table II. However, it is

TABLE II

OBSERVED AND CALCULATED RATE CONSTANTS IN THE BROMINATION OF $XC_6H_4C(=CH_2)C_6H_4Y$, USING THE EXPRESSION LOG $k/k_0 = \sigma^+ + \sigma$

Compd	X	Y	σ^+_X	σ_Y	Log k^a_{calcd}	Log k_{obsd}
2	*p*-MeO	*p*-Me	−0.778	−0.170	6.259	5.989
	p-Me	*p*-MeO	−0.311	−0.268	5.056	
b	*p*-MeO	H	−0.778	0.000	5.705	5.578
	H	*p*-MeO	0.000	−0.268	4.052	
4	*p*-MeO	*p*-Br	−0.778	+0.232	4.949	5.028
	p-Br	*p*-MeO	+0.150	−0.268	3.553	
9	*p*-Me	*p*-F	−0.311	+0.062	3.980	3.997
	p-F	*p*-Me	−0.073	−0.170	3.961	
13	*p*-Me	*p*-Br	−0.311	+0.232	3.426	3.614
	p-Br	*p*-Me	+0.150	−0.170	3.234	

[a] Log $k_{calcd} = -3.26(\sigma^+_X + \sigma_Y) + 3.169$; k in l. mol^{-1} sec^{-1}. [b] Data from Table I of ref 1.

not possible to bring the methoxy nitro compounds onto this correlation by using any combination of σ and σ^+ values.

A more exact test of this model would assume that the substituent X with the largest electron-donating power by resonance still acts in a disubstituted compound with the same σ value used when it alone was present. The monosubstituted compounds have been shown to fit the equation log $k/k_0 = -3.57$ $(\sigma_0 + 0.84\ \Delta\sigma^+)$ to a high degree of accuracy.[1] The σ_Y value (which refers to the second substituent Y), required to duplicate the observed kinetic results for the disubstituted compounds, may then be calculated (Table III). If the assumptions that ρ is constant throughout

TABLE III

CALCULATED σ AND R VALUES FOR DISUBSTITUTED 1,1-DIPHENYLETHYLENES, $XC_6H_4C(=CH_2)C_6H_4Y$

Compd	X	Y	σ_Y[a]	$\sigma_{total} - \Sigma\sigma^0$[b]	R[c]
1	*p*-MeO	*p*-MeO	−0.20	−0.72	0.54
2	*p*-MeO	*p*-Me	−0.10	−0.45	0.53
4	*p*-MeO	*p*-Br	+0.17	−0.70	0.85
5	*p*-Me	*p*-Me	−0.21	−0.24	0.65
9	*p*-Me	*p*-F	+0.06	−0.30	0.65
10	*p*-MeO	*m*-NO_2	+0.50	−0.79	1.15
11	*p*-MeO	*p*-NO_2	+0.51	−0.87	1.28
13	*p*-Me	*p*-Br	+0.18	−0.28	0.83
15	*p*-F	*p*-F	+0.07	−0.38	0.66
20	*p*-Cl	*p*-Cl	+0.18	−0.24	0.73
21	*p*-Br	*p*-Br	+0.18	−0.25	0.85

[a] $\sigma_Y = \sigma_{total} - (0.84\ \Delta\sigma_X^+ + \sigma_X^0)$. [b] $\sigma_{total} = -(\log k - 3.25)/3.57$. [c] $R = (\sigma_{total} - \Sigma\sigma^0)/\Sigma\Delta\sigma^+$.

the series and that IX is a good model for the transition state are correct, one would expect that (1) σ_Y for a given substituent would be constant and independent of the nature of X, and (2) that the σ_Y values calculated would be close to the ordinary Hammett σ

values. It is clear from the data listed in Table III that neither of these conditions is observed exactly. Thus, taking *p*-bromo (σ = +0.232) as an example, σ_Y is (+0.17, +0.18, +0.18) with X (*p*-MeO, *p*-Me, *p*-Br). However, if a limited set of data is chosen (ignoring again the methoxy nitro compounds), there is approximate agreement with 1 and 2; this accounts for the success of the simple log $k/k_0 = \rho(\sigma^+ + \sigma)$ treatment used previously. A more detailed treatment of the data cannot be carried out without assuming that ρ varies.

(2) The alternative approach, using structure VIII as a model, would assume that the system has a relatively rigid configuration in which the two rings were twisted equally out of the plane in the olefin and retained this structure in the transition state of the bromination reaction, independent of the substituents present in the aromatic rings.[29] In this case the substituents in both mono- and disubstituted compounds would each transmit by resonance the same fraction for the stabilization of the carbonium ion. Yukawa and Tsuno[30] have developed a modified form of the Hammett equation applicable to electrophilic reactions for which the Brown–Okamoto σ^+ values either over- or undercorrect for the resonance contributions of the substituents. In the equation

$$\log k/k_0 = \rho(\sigma^0 + R\Delta\sigma^+)$$

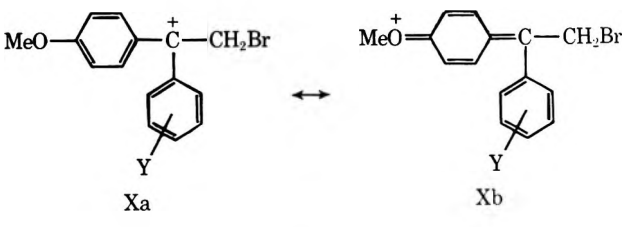
the extra parameter R is a reaction constant indicative of the degree of resonance in the transition state, and $\Delta\sigma^+$ ($\sigma^+ - \sigma^0$) is the measure of the resonance contribution of a given substituent. Applying this equation to the results obtained for the bromination of 32 1,1-diarylethylenes (using $\Sigma\sigma^0$ and $\Sigma\Delta\sigma^+$ in place of σ^0 and $\Delta\sigma^+$) gave $\rho = -3.54$, $R = 0.59$ with $r = 0.991$ and $s = 0.714$. The nitro methoxy compounds again deviated significantly and were omitted from this correlation.

Although this ρ value corresponds almost exactly to that obtained using the meta-substituted compounds alone,[1] the R value is decidedly different from that reported for the monosubstituted compounds (0.84 *vs.* 0.59); it is difficult to rationalize how this might be so. This low R implies that a relatively small fraction of resonance is transmitted from the substituent in the transition state. If this is related to the angle of twist using the $\cos^2\phi$ relationship, it is found that ϕ is *ca.* 40° for each ring. This is a significantly larger angle than any of the estimates on 1,1-diphenylethylenes. Moreover, the correlation coefficient shows that this is a less precise treatment of the data and thus does not justify the introduction of the extra parameter R. More seriously, the mono- and disubstituted compounds deviate from the relationship in opposite directions: it is clear that the closeness of the fit observed, such as it is, is due rather to the large body of data used in the computation than to the fact that the Yukawa–Tsuno equation is able to deal with the data for the mono- and disubstituted compounds simultaneously.

Simple inductive effects appear to be additive for substituents in both rings. Thus the five di-meta-substituted 1,1-diphenylethylenes (including both symmetrically and unsymmetrically substituted compounds) are excellently correlated with σ_m to give much the same ρ (−3.65, with $r = 0.997$, $s = 0.377$) as obtained for mono-meta substitution. This fact was used to rigorously test the approach 2 as follows. Using the Yukawa–Tsuno equation in the form log $k/k_0 = -3.57\,[\Sigma\sigma^0 + R\Sigma\Delta\sigma^+]$, the fractional resonance contribution, R, for each disubstituted compound was calculated (Table III). If there is no interaction between the substituents, then R should be constant throughout the series. Although this is true to a very limited extent, particularly when $\sigma_{total} - \Sigma\sigma^0$ is not large, it is clear that R seems to vary in a general way with both substituents. Thus, when X = MeO, R is successively equal to 0.54, 0.53, 0.83, 0.85, and 1.28 when the second substituent Y is MeO, Me, H, Br, NO_2.

Thus we conclude, from a consideration of stereochemical factors alone, that in the transition state of the bromination of 1,1-diphenylethylenes, the favored configuration is unsymmetrical. One of the aryl rings is conjugated with the vacant p orbital of the forming carbonium ion, the other being rotated through a large enough angle so that substituents in this ring do not conjugatively stabilize the forming carbonium ion. This description places the onus of the observed non-additivity of substituent effects on the geometry of the system and on the magnitude of the σ constants involved, rather than on ρ, which is assumed to be constant throughout. However, the deviations shown by 1-(*p*-methoxyphenyl)-1-(*m*- and *p*-nitrophenyl)ethylenes in particular cannot be accommodated using any reasonable combination of σ values.

B. Multiple ρ Treatment.—It is therefore proposed that the presence of a substituent, particularly one capable of electron donation by resonance, in the aromatic ring so alters the charge distribution in the transition state that the second substituent in the other ring then interacts with a charge different from that prevailing if the substituent were alone. From a theoretical point of view, simple additivity of substituent effects is to be expected in those reactions in which the free-energy plot is precisely linear,[31] and this has in fact often been observed.[32] However, in the presence of, say, a *p*-methoxy group a large fraction of the charge would be delocalized onto the substituent (as Xb). The sensitivity of the bromination reaction



Xa Xb

to the variation of the second substituent Y, now more remote from the positive charge, is much reduced. The change in the response of the reaction to the variation of Y would be expected to be some function of

(29) The presence of a *p*-methoxy group in one of the rings in 1,1-diphenylethylene brings about a small separation of the nmr signals for the terminal olefinic protons (with *p*-bromo or *p*-methyl substituents, the protons remain equivalent). Van der Linde, *et al.*,[19] therefore concluded that the effect of substituents on the conformations of 1,1-diphenylethylenes is not very great.

(30) Y. Tsuno, I. Isabata, and Y. Yukawa, *Bull. Chem. Soc. Jap.*, **32**, 960 (1959); Y. Yukawa and Y. Tsuno, *ibid.*, **32**, 965, 971 (1959); *J. Chem. Soc. Jap.*, **86**, 875 (1965).

(31) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, p 192.

(32) H. H. Jaffe, *Chem. Rev.*, **53**, 191 (1953).

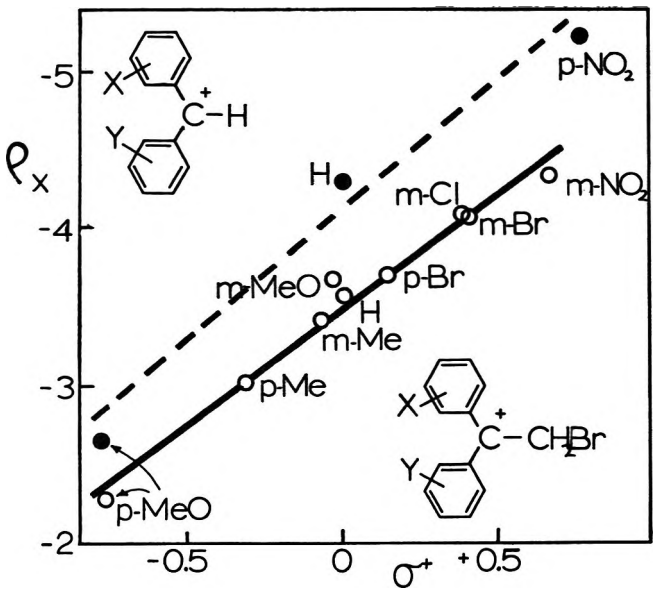


Figure 2.—Plots of (a) the ρ values (●) derived in Table V for the solvolysis of $XC_6H_4(Ar)CHCl$ in 90% acetone (X = constant for each of the points, while the substituent in Ar varies) and (b) ρ values (○) obtained similarly for the bromination of $XC_6H_4(Ar)C = CH_2$ in methanol *vs.* the σ^+ value of the substituent X (Table IV).

the electron-withdrawing or donating power (as measured by its σ^+ value) of the first substituent. As a subsidiary effect, for maximum delocalization (as in Xb) the ring containing the *p*-methoxy group would have to be in the plane of the carbonium ion;[27] in this situation Y cannot stabilize the transition state to the same degree as in the absence of the *p*-methoxy group, *i.e.*, the para positions of the two rings become nonequivalent.

We have therefore examined the reactivity of various groups of compounds in which one of the substituents (X) was held constant while the other (Y) was varied. Since the σ value appropriate to the second substituent Y is indefinite, two series of compounds (X = *p*-MeO and *p*-Me) which included extensive data for (Y =) meta substituents were employed. Since the meta substituents act largely inductively, their influence on the rate of bromination is independent of the angle of rotation of the second ring.[27] The calculated ρ values for the variation of Y when X = *p*-MeO and *p*-Me are −2.27 and −3.03, respectively (see Table IV).

For the other series of compounds in Table IV in which the substituent is held constant and Y varied, a sufficient number of meta-substituted compounds were not available. In these cases the assumption was made that the value of R is the same (0.84) as that obtained for the correlation of the monosubstituted derivatives (*i.e.*, where X = H).[1] This is not unreasonable in view of the fact that none of the substituents Y involved are capable of strong resonance stabilization of the carbonium ion center. The calculated ρ values thus obtained (which refer to the constant substituent X) are listed in Table IV; satisfactory correlations were obtained in all cases.

The well-defined value of ρ obtained when the constant substituent X = *p*-MeO (*viz.*, −2.27) permits the use of the Yukawa–Tsuno equation to calculate the R value applicable to substituents in the second ring Y which are able to further stabilize the developing carbonium ion by conjugation (*i.e.*, $\Delta\sigma^+ > 0$). Using data for compounds **1**, **2**, and **4** (Table I) an R value of 0.4 is obtained. This value is significantly lower than that obtained (0.84) for the monosubstituted ethylenes.[1] This must mean that the second less electron-donating substituent interacts conjugatively with the developing charge to a smaller extent (but not negligibly) than the first *p*-methoxy substituent. Assuming that R = 1.0 when the aryl ring is coplanar with the carbonium ion[33] and that a $\cos^2\phi$ relationship holds for the effect of the angle of rotation ϕ upon the transmission of conjugative effects, then R = 0.84 and 0.4 represent angles of 23 and 49°, respectively. Thus it appears that (as tentatively suggested above), a substituent capable of strong conjugation with the reaction center distorts the equivalence of the two aryl rings in the transition state.

Saturation of Resonance.—The ρ values obtained (Table IV) are related in a general way to the electron disturbance of the substituent X which is retained constant (as measured by its σ^+ value); see Figure 2. By extrapolation from these data, when $\sigma^+ \sim -2.2$ then ρ = 0, implying that, when one of the aryl groups contained a substituent with such (or greater) electron-donating power, the rate of bromination of the ethylene would be independent of the nature of further substitution; *i.e.*, the system would be "saturated."

We have applied a similar treatment to the data of Fox and Kohnstam[34] for the solvolysis of 1-aryl-1-(*p*-methoxy, *p*-nitro, and unsubstituted phenyl) carbinyl chlorides, using the Yukawa–Tsuno treatment (see Table V). The ρ values again differ as the first

TABLE IV

CALCULATED ρ VALUES FOR THE VARIATION OF SUBSTITUENT Y WITH SUBSTITUENT X HELD CONSTANT [DATA FROM BROMINATION OF ETHYLENES $XC_6H_4C(=CH_2)C_6H_4Y$][a]

Substituent X	ρ	r	σ^+ (X)	Substituents Y used
p-MeO	−2.27	0.999	−0.78	H, *p*-NO_2, *m*-NO_2, *m*-Br, *m*-Cl, *m*-Me
p-Me	−3.03	0.996	−0.311	H, *m*-NO_2, *m*-Br, *m*-Me
m-Me	−3.42	0.999	−0.066	*p*-MeO, *p*-Me, H, *m*-Me, *m*-F
m-MeO	−3.69	0.999	−0.048	*m*-MeO, *m*-Br, H
p-Br	−3.67	0.999	+0.150	*p*-MeO, *p*-Me, H
m-Cl	−4.08	0.999	+0.399	*p*-Me, *m*-Cl, H
m-Br	−4.05	0.994	+0.405	*p*-MeO, *p*-Me, *m*-MeO
m-NO_2	−4.65	0.999	+0.674	*p*-MeO, *p*-Me, H
H	−3.57	0.999	0	See ref 1

[a] Kinetic data from Table I and Table I of ref 1.

TABLE V

CALCULATED REACTION CONSTANTS FOR THE SOLVOLYSIS OF 1-(*p*-X-PHENYL)-1-ARYLCARBINYL CHLORIDES[a]

Substituent X	ρ[b]	R	r
MeO	−2.63	1.20	0.999
H	−4.31	1.44	0.996
NO_2	−5.26	1.50	0.996

[a] Calculated from data in J. R. Fox and G. Kohnstam, *Proc. Chem. Soc.*, 115 (1964).

(33) This assumption may be in error, since values of R considerably in excess of unity have been reported; see, for example, J. E. Dubois and A. F. Hegarty, *J. Chem. Soc. B*, 638 (1969).

(34) J. R. Fox and G. Kohnstam, *Proc. Chem. Soc.*, 115 (1964).

substituent is changed and decrease with increased electron-donating power of the constant substituent (see Figure 2), *i.e.*, in the order p-NO_2 > H > p-MeO. Although no clear distinction is apparent in this case between the use of σ and σ^+ values for the second substituent, the resonance interaction constant, R, does decrease when X = OMe, showing that in this case less resonance stabilization by the substituents Y is involved than when X = H or p-NO_2.

The data of Nishida[12] for the solvolysis of benzhydryl chlorides in methanol differs from that of Fox and Kohnstam[34] in that plots of log k *vs.* σ^+ were obtained with little curvature (which implies that R = 1.0 throughout). However, the same decrease in sensitivity to substituent variation on the introduction of electron-donating groups is noted. The general features of a plot of ρ_X *vs.* σ^+_X were the same[35] (as Figure 2) except that a folded line about $\sigma^+ = 0$ was obtained.

It is possible that this effect (whereby substantial delocalization of charge onto a side chain from the reaction center causes a decrease in the sensitivity of the reaction to the effect of a second substituent now placed further from the charged center) is quite general, but only observed[11] when compounds differing greatly in in reactivity are studied. It is operative not only when the two substituents concerned are on different rings (although, of necessity, it is exaggerated in this case), but also when both substituents are on the same ring. Thus in the bromination of substituted benzenes (PhX)) the sensitivities to further substituent variation decrease in the order X = H > Me > MeO > NMe_2; here again a similar general relationship can be obtained between the ρ values calculated for the substituent X and its σ^+ value.[36]

In conclusion, although clear nonadditivity of substituent effects is evident in the bromination of 1,1-diphenylethylenes, it is not possible to attribute this entirely to the stereochemistry of the system. Apparently no single ρ value is involved throughout the series, but various ρ values are obtained with good precision when one of the rings (say Ar in VI) is kept constant while substituents in the second ring (Ar′) are varied. The multiple ρ values thus obtained are close to the value for monosubstitution (VI, Ar = Ph) only when the substituent in the Ar ring does not differ greatly in electron disturbance from hydrogen (*e.g.*, Ar = p-BrC_6H_5 or m-MeC_6H_4), accounting for the apparently good correlations previously obtained with more limited data.[37] Use of the variable ρ value for the first ring accounts accurately for the data for the bromination of all multiply substituted 1,1-diphenylethylenes and the solvolysis of benzhydryl chlorides and clearly deserves to be applied in other similar cases.

(35) Moreover, much the same substituents [m-Me, p-Br in the present study, m-Me, p-Cl in solvolysis, S. Nishida, *J. Org. Chem.*, **32**, 2695 (1967)] gave ρ values close to that observed for the monosubstituted compounds.

(36) Using ρ = −12.1 for the bromination of benzenes [L. M. Stock and H. C. Brown, *Advan. Phys. Org. Chem.*, **1**, 35 (1963)]; ρ = −10.7 for toluenes [J. E. Dubois, P. Alcais, and F. Rothenburg, *J. Org. Chem.*, **33**, 439 (1968)]; ρ = −6.76 for anisoles [J. E. Dubois and J. J. Aaron, *J. Chim. Phys.*, 1354 (1964)]; and ρ = −2.2 for dimethylanilines [J. E. Dubois and R. Uzan, *Bull. Soc. Chim. Fr.*, 598 (1971)]. A plot of ρ *vs.* σ^+ gives a reasonable correlation with a slope of −5.23 (r = 0.983, s = 1.51), in spite of the approximation involved in the determination of ρ.

(37) S. Altscher, R. Baltzly, and S. W. Blackman, *J. Amer. Chem. Soc.*, **74**, 3649 (1952); S. Nishida, *J. Org. Chem.*, **32**, 2692 (1967).

Experimental Section

Substrates.—The diphenylethylenes were prepared by the general methods involving Grignard reagents which have previously been described.[1] In addition, a further method (an example of which follows) was found to be applicable to the synthesis of symmetrically disubstituted olefins. Those olefins with nitro substituents were prepared by a modification of the Wittig reaction. Data for the olefins are listed in Table VI.

TABLE VI

ANALYTICAL AND PHYSICAL DATA FOR 1,1-DIARYLETHYLENES [$XC_6H_4C(=CH_2)C_6H_4Y$]

X	Y	Bp, °C (mm), or mp, °C	Yield, %
p-MeO	p-Me	74–74.5[a]	63
p-Br	p-MeO	86–87[a,b]	55
p-F	p-Me	173–175 (24)[a]	40
p-MeO	m-NO_2	178 (0.5)[a,c]	25
p-MeO	p-NO_2	85.5[a,d]	30
m-Me	m-Me	183–185 (25)[a]	46
p-Br	p-Me	64.5–65[a]	63
m-MeO	m-MeO	228–230 (30)[a]	20
m-F	m-Me	98 (0.5)[a]	60
m-Br	m-MeO	150 (0.5)[a,e]	55
m-Cl	m-Cl	150 (0.5)[a]	55
p-MeO	m-Br	145–149 (0.3)[a,f]	56
p-MeO	m-Cl	132 (0.2)[a,g] (mp 27)	50
m-NO_2	p-Me	72[a]	11
p-Me	m-Br	43[a]	53
p-MeO	m-Me	152–155 (0.5)[a]	9
p-Me	m-Me	128 (1.5)[a]	77

[a] Satisfactory analytical data (±0.35%) were reported for these compounds: Ed. [b] Recrystallized once from petroleum ether (bp 40–60°) and then from absolute ethanol. [c] Distillation at this temperature caused decomposition; this olefin was purified on a silica gel column using benzene–hexane (1:1) as eluent. [d] The oily residue obtained on evaporation of the chloroform was purified by chromatography (silica gel, 1:2 benzene–hexane as eluent). [e] Calcd: MeO, 10.7. Found: MeO, 10.6. [f] Calcd: MeO, 10.7. Found: MeO, 10.9. [g] Calcd: MeO, 12.7. Found: MeO, 12.6.

1,1-Di(*m*-tolyl)ethylene.—The Grignard reagent, prepared from magnesium (5.0 g) and m-bromotoluene (34.2 g) in 150 ml of anhydrous ether, was treated at 0° with a solution of ethyl acetate (8.8 g) in 10 ml of ether. After standing for 12 hr at room temperature, the mixture was refluxed for 30 min and, on cooling, the adduct was decomposed with dilute sulfuric acid–ice. The ether layer was washed with water (2 × 20 ml) and then with a saturated sodium carbonate solution (20 ml). After drying ($MgSO_4$), the ether was evaporated and the oily residue was distilled, bp 175–180° (20 mm), with spontaneous dehydration. To remove the small amount of water that distilled, dry ether (10 ml) was added to the distillate, and the solution was dried over calcium chloride and redistilled, bp 185–187° (27 mm), yielding 9.0 g of the ethylene.

1-(*m*-Nitrophenyl)-1-(*p*-tolyl)ethylene.—To a suspension of NaH [prepared by washing 2.4 g of NaH (50%) in mineral oil with hexane] in 100 ml of dry DMF was added 10 g of triethyl phosphonoacetate. The temperature was kept at 20° during the addition. When the evolution of hydrogen gas had ceased, 10 g of 4-methyl-3′-nitrobenzophenone was added and the mixture was heated to 120° for 12 hr. The red mixture was decomposed with 1.5 l. of cold water and extracted with 3 × 300 ml of CH_2Cl_2. The organic layer was washed twice with water, dried over $MgSO_4$, and concentrated. The deep brown residue was taken in 100 ml of 10% methanolic KOH and refluxed for 2 hr, diluted with water, and extracted with 2 × 50 ml of CH_2Cl_2 to remove nonacidic material. The aqueous solution was acidified and extracted with 2 × 100 ml of CH_2Cl_2, washed with water, and dried. Removal of the solvent gave 3.5 g of a solid which was taken up in 20 ml of quinoline. Cu powder was added and the

mixture was refluxed for 3 hr to effect decarboxylation, diluted with 10% HCl, and extracted with 2 × 50 ml of CH_2Cl_2. The organic layer was washed with water and dried over $MgSO_4$. Removal of the solvent and chromatography of the residue on Florisil (eluent hexane–ether) gave 1.1 g of the ethylene, mp 72° (from petroleum ether, bp 40–60°); see Table VI for analytical data.

Kinetic Measurements.—The kinetic measurements were carried out at 25° in methanol containing 0.20 *M* sodium bromide. The purification procedure used for the solvent has previously been described.[1] It has been shown previously that under these conditions Br_2 is the only electrophile of importance. Each experiment was repeated a minimum of five times and the rate values listed in Table I are accurate to better than ±2% (compounds **5**–**23**) or ±4% (compounds **1**–**4**).

The various electrometric methods used to follow the disappearance of bromine at low concentration have been described in detail elsewhere.[38] To ensure the accuracy of the rate constants listed, comparison was continually made with substrates whose bromination rates have been well established (see ref 1 for details).

Registry No.—**1**, 4356-69-8; **2**, 13392-76-2; **3**, 13392-77-3; **4**, 34564-83-5; **5**, 2919-20-2; **6**, 34564-84-6; **7**, 34564-85-7; **8**, 22057-87-0; **9**, 365-23-1; **10**, 34564-88-0; **11**, 28358-68-1; **12**, 10605-48-8; **13**, 34564-89-1; **14**, 1488-34-2; **15**, 6175-14-0; **16**, 34564-91-5; **17**, 34564-92-6; **18**, 28358-71-6; **19**, 34564-93-7; **20**, 2642-81-1; **21**, 10605-43-3; **22**, 28358-69-2; **23**, 29265-85-8.

(38) R. P. Bell and D. Dolman, *J. Chem. Soc. B*, 500 (1968); J. E. Dubois and G. Mouvier, *C. R. Acad. Sci.*, **255**, 1104 (1962); J. E. Dubois, P. Alcais, and G. Barbier, *J. Electroanal. Chem.*, **8**, 359 (1964); see also ref 1.

Comparisons of the Reactions of Butadiene with Chlorine, Bromine, Acetyl Hypochlorite, and Acetyl Hypobromite

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The addition reactions of butadiene with the indicated electrophiles were studied in various solvents with the object being to gain additional insights into the nature of the bonding in the halonium ion intermediates. The following observations were made. (a) All of the electrophiles reacted with butadiene to give both 1,2 and 1,4 addition. The hypohalites (ClOAc, but particularly BrOAc), however, gave considerably less 1,4 addition than the halogens. (b) The 1,2-addition product from the hypohalites (ClOAc and BrOAc) showed exclusively Markovnikov orientation. (c) A study of the bromination and chlorination of butadiene in acetic acid is reported. Solvent incorporation is much greater in chlorination than bromination. (d) There is considerably more attack by acetic acid at the terminal vinylic carbon atom during chlorination than during bromination. Also in nonpolar solvents acetyl hypochlorite gave more 1,4 addition than acetyl hypobromite. (e) The bromine systems (Br_2 and BrOAc) show a general trend toward greater 1,4 addition as the solvent polarity increases, whereas the chlorine systems are insensitive to solvent polarity. On the basis of some of the above observations, we suggest that the intermediate chloronium ion formed in the addition of chlorine or acetyl hypochlorite to butadiene has extensive delocalization of the charge into the neighboring vinylic system. This is in contrast to the bromonium ion which we have described previously (and also supported by this study) as having the charge shared between the secondary carbon and bromine atoms with little delocalization into the vinylic system.

The most probable reactions of the electrophiles and butadiene, and the products expected from the reactions, are outlined below, in which X refers to Cl and Br, and Y represents Cl, Br, and OAc.

$$CH_2{=}CHCH{=}CH_2 \xrightarrow{X\text{–}Y} CH_2CHCH{=}CH_2 + XCH_2CH{=}CHCH_2Y$$
(X and Y on the first product)

	1,2 addition	1,4 addition[2]
X = Y = Cl	3,4-dichloro-1-butene (**1**)	1,4-dichloro-2-butene (**5**)
X = Y = Br	3,4-dibromo-1-butene (**2**)	1,4-dibromo-2-butene (**6**)
X = Cl; Y = OAc	3-acetoxy-4-chloro-1-butene (**3**)	1-acetoxy-4-chloro-2-butene (**7**)
X = Br; Y = OAc	3-acetoxy-4-bromo-1-butene (**4**)	1-acetoxy-4-bromo-2-butene (**8**)

We hoped that this investigation would provide additional insights[3] into the nature of the bonding in the halonium ion intermediates involved in these reactions. In particular, we focused our attention on the following areas: (a) to determine if anti-Markovnikov products are formed when ClOAc and BrOAc are added to butadiene; (b) to study the variation in the 1,2- to 1,4-product ratios when the anion is changed but the cation remains the same (Cl_2, ClOAc and Br_2, BrOAc), and when only the cation is changed (BrOAc, ClOAc); (c) to examine the effect of solvent polarity on these reactions; and (d) to compare the amount and position of solvent attack when butadiene is brominated and chlorinated in acetic acid.

No investigations of the reactions of acetyl hypochlorite or hypobromite with butadiene have appeared in the literature. The chlorination[2] and bromination[4] of butadiene has recently been studied, but only in nonpolar solvents.

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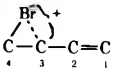
(2) The trans isomers would be expected, since previous studies on butadiene have shown that only trace amounts of the cis isomers are found during bromination,[4a] bromination in methanol (methoxy bromide formation),[3a] and chlorination [M. L. Poutsma, *J. Org. Chem.*, **31**, 4167 (1966)].

(3) On the basis of our previous studies [(a) V. L. Heasley and P. H. Chamberlain, *J. Org. Chem.*, **35**, 539 (1970); (b) V. L. Heasley, G. E. Heasley, S. K. Taylor, and C. L. Frye, *ibid.*, **35**, 2967 (1970)] we postulate that the halonium ion intermediate involved in the bromination of butadiene is best represented as follows.



(4) (a) V. L. Heasley and S. Taylor, *J. Org. Chem.*, **34**, 2779 (1969); (b) L. F. Hatch, P. D. Gardner, and R. E. Gilbert, *J. Amer. Chem. Soc.*, **81**, 5943 (1956).

Results and Discussion

Table I contains a summary of the data on the chlorination and bromination of butadiene in several solvents, and under kinetic control.

TABLE I
ADDITION OF Br_2 AND Cl_2 TO BUTADIENE IN VARIOUS SOLVENTS AT $-10°$

Solvent	Electrophile	1,2/1,4 Ratio	Yield, %
n-Pentane[a]	Br_2	2.2	105
Carbon tetrachloride[a]	Br_2	1.3	100
Dichloromethane	Br_2	0.39	107
Acetonitrile	Br_2	0.67	100
Nitromethane	Br_2	0.35	85
Methanol[b]	Br_2	2.2	
n-Pentane	Cl_2	1.2	56
Carbon tetrachloride	Cl_2	1.3	77
Dichloromethane	Cl_2	1.3	61
Acetonitrile	Cl_2		*c*
Nitromethane	Cl_2		*d*

[a] Hatch, *et al.*,[4b] report the following 1,2/1,4 ratios for *n*-hexane and carbon tetrachloride, respectively: 1.1 and 1.0. [b] See ref 3a. [c] Only a very small amount of dichlorides was formed in this reaction. [d] Result is not reported since the yield is low and unidentified products were formed.

Data concerning the addition of acetyl hypochlorite and acetyl hypobromite to butadiene are listed in Table II. The results in Tables I and II indicate that

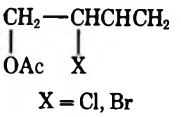
TABLE II
ADDITION OF ClOAc AND BrOAc TO BUTADIENE IN VARIOUS SOLVENTS AT $-10°$

Solvent	Electrophile	1,2/1,4 Ratio	Yield, %
n-Pentane	BrOAc	6.7	53
Carbon tetrachloride	BrOAc	6.7	52
Acetic acid[a]	BrOAc	5.3	57
Dichloromethane	BrOAc	4.9	55
Acetonitrile	BrOAc	2.4	36
Nitromethane	BrOAc	3.0	31
n-Pentane	ClOAc	2.8	48
Carbon tetrachloride	ClOAc	2.6	49
Acetic acid[a]	ClOAc	2.0	50
Dichloromethane	ClOAc	2.4	38
Acetonitrile	ClOAc	1.3	15
Nitromethane	ClOAc		*b*

[a] The temperature was 15° in this case. [b] Result is not reported since the yield was low and unidentified products were formed.

the hypohalites do not give so much 1,4 addition as the halogens do. This is especially pronounced in the case of acetyl hypobromite. It has recently been suggested that 1,4 addition of electrophiles to dienes occurs by an S_N2' attack of the anion on the 1 carbon atom of the halonium ion.[5] If this is correct, the chloride and bromide ions should migrate more readily to the 1 carbon atom, since they should experience weaker bonding to the cation (halogen end of the molecule) in the ion pair than the acetate ion.

We also attempted to determine whether the acetate ion in the addition of acetyl hypochlorite and hypobromite could attack at the 4 carbon atom and give the anti-Markovnikov addition products shown below.



The syntheses of the above acetoxy halides have previously been reported.[6] We established unequivocally by infrared and nmr analyses that they were absent in the reaction product resulting from the addition of hypohalites to butadiene. Mueller and Butler[7] reported earlier that in the addition of methanesulfenyl chloride to butadiene the episulfonium ion intermediate is opened exclusively at the secondary carbon atom. Therefore, our observation is not unexpected, since the halonium ion intermediates involved in the addition of the hypohalites should possess even greater unsymmetrical bonding than the episulfonium ions, and should make anti-Marovnikov opening of the ring more difficult.

A summary of the results on the addition of bromine and chlorine to butadiene in acetic acid is recorded in Table III. As is indicated in Table III, chlorination

TABLE III
ADDITION OF Br_2 AND Cl_2 TO BUTADIENE IN ACETIC ACID AT 15°

	1,2/1,4 Ratio		Yield, %	
Electrophile	Dihalides	Acetoxy halides	Dihalides	Acetoxy halides
Br_2	0.26	9.0	87	10
Cl_2	1.3	1.8	33	53

gives dichlorides **1** and **5** and acetoxy chlorides **3** and **7**; dibromides **2** and **6** and acetoxy bromides **4** and **8** are formed during bromination. Acetic acid incorporation, however, is much greater during chlorination than bromination. This difference may be due to greater carbonium ion character in the intermediate involved in chlorination.[8] It should also be mentioned that the lower yields with the chlorine systems (Cl_2 and ClOAc) in acetonitrile probably result from extensive solvent incorporation.

The 1,2/1,4 ratios for the acetoxy halides and dihalides in Table III reveal further interesting insights into the nature of the carbonium ion intermediates involved in these reactions. The extent of the attack by acetic acid at the 1 carbon atom is much greater in chlorination (to give **7**) than in bromination (to give **8**). Also, acetyl hypochlorite (Table II) in nonpolar solvents[9] such as *n*-pentane and carbon tetrachloride also shows greater reactivity at the terminal carbon

(5) (a) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," McGraw-Hill, New York, N. Y., 1968, p 572. (b) At present there is no experimental evidence that 1,4 addition of electrophiles to dienes occurs by attack of the anion at the terminal carbon of the vinylic system. Simultaneous addition to the terminal carbons of the s-trans conformation of the diene could also account for the results. We are currently investigating this problem.

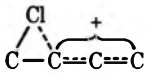
(6) A. A. Petrov, *J. Gen. Chem. USSR*, **11**, 991 (1941).

(7) W. H. Mueller and P. E. Butler, *J. Org. Chem.*, **33**, 2642 (1968).

(8) Less solvent incorporation during bromination could result from the fact that the bromide is more nucleophilic than the chloride ion and, therefore, more dibromide is formed.

(9) According to Buckles and coworkers [*J. Org. Chem.*, **27**, 4523 (1962)] the charge on a carbonium ion system will be dispersed to the greatest extent in solvents with low dielectric constants.

atom of the vinylic system than does acetyl hypobromite. These observations suggest that the intermediate in the chlorination of butadiene (and perhaps in the addition of acetyl hypochlorite) has considerably greater carbonium ion character at the 1 carbon atom than does the corresponding intermediate in the bromination of butadiene. On the basis of these studies, we are suggesting that the chloronium ion from butadiene has much more extensive dispersal of charge into the vinylic system than the corresponding bromonium ion, and may be represented as follows.



With the exception of the solvent methanol, the bromine systems (Br_2 and BrOAc, Tables I and II) show a general trend toward greater 1,4 addition as the solvent polarity is increased. On the other hand, the chlorine systems are insensitive to the polarity of the solvent. Our results on the effect of solvent polarity on bromination of butadiene are in general agreement with an early study by Farmer, *et al.*[10] In a more recent publication on this subject, Hatch[4b] and coworkers make the statement that the ratio of 1,2 to 1,4 addition is not effected by solvent polarity. Actually these authors only investigated the reaction in solvents of rather low polarity, and were not in a position to make this assumption.[11] It is clear from our investigations that the 1,4-dibromide **6** can be both the main product and the kinetically controlled product if the solvent is sufficiently polar.[12]

Experimental Section

Materials.—All solvents and reagents were obtained commercially in high purity unless otherwise indicated. The butadiene was Matheson's instrument grade, 99.5%. Acetyl hypochlorite was prepared according to the method of Evans, *et al.*[13] Acetyl hypobromite was prepared as described by Haubenstock and VanderWerf,[14] with the exception that the acetyl hypobromite–carbon tetrachloride solution was isolated from the silver bromide by filtration. 3,4-Dibromo-1-butene (**2**) and *trans*-1,4-dibromo-2-butene (**6**) were synthesized as described by Hatch, *et al.*[4b] *trans*-1,4-Dichloro-2-butene (**5**) was obtained commercially as a "Baker Analyzed" reagent.

3,4-Dichloro-1-butene (1).—**1** was prepared by chlorination of butadiene in dichloromethane and was separated from **5** by fractional distillation. Its structure was confirmed by the boiling point, bp 48° (52 mm) [lit.[15] pp 45° (40 mm)], and the ir spectrum (terminal vinyl, 936 and 984 cm^{-1}).

3-Acetoxy-4-chloro-1-butene (3), 1-Acetoxy-4-chloro-2-butene (7), 3-Acetoxy-4-bromo-1-butene (4), and 1-Acetoxy-4-bromo-2-butene (8).—These compounds were isolated from large-scale reactions of the appropriate hypohalite and butadiene using fractional distillation. Their structures were established by ir and nmr analyses. The pertinent physical data confirming the structures for these compounds are summarized in Table IV.

TABLE IV

PHYSICAL DATA ON THE ACETOXY HALIDES (3, 4, 7, and 8)

Compd	Bp, °C (mm)	Ir, cm^{-1} [a]	Nmr, δ [a]
3	48–50 (8)	C=O (1755)	2.20 (s, 3, CH_3)
		H_2C=CH	3.79 (d, 2, CH_2)
		(942, 988)	5.43–6.28 (m, 4, CHCH=CH_2)
4	30–31	C=O (1755)	2.17 (s, 3, CH_3)
	(0.35)	H_2C=CH	3.70 (d, 2, CH_2)
		(942, 989)	5.38–6.44 (m, 4, CHCH=CH_2)
7	75–80 (7)	C=O (1750)	2.12 (s, 3, CH_3)
		trans HC=CH	4.22 (m, 2, CH_2)
		(970)	4.75 (m, 2, CH_2)
			Vinyl hydrogens[b]
8	49 (0.35)	C=O (1750)	2.11 (s, 2, CH_3)
		trans HC=CH	4.11 (m, 2, CH_2)
		(969)	4.73 (m, 2, CH_2)
			Vinyl hydrogens[b]

[a] The ir and nmr spectra were made in CCl_4. [b] The samples of **7** and **8** which were used for the nmr spectra were contaminated with significant amounts of **3** and **4**. Therefore the vinyl region was indeterminable.

Reaction Conditions.—The initial mole fractions of butadiene ranged from 0.025 to 0.05, and were kept at a low level in order to avoid radical reactions.[16] The magnitude of the reaction solutions varied from 25 to 35 ml, depending on the concentration of hypohalite solution. Since the hypohalites were prepared in carbon tetrachloride solution, the halogens were also added in this solvent. The concentrations of the solutions of acetyl hypochlorite and acetyl hypobromite were, respectively, *ca.* 0.70 and 0.30 *M*; the halogen concentrations were made to correspond to the respective hypohalite. The product composition did not seem to be influenced by the rate of addition of either the halogens or the hypohalites. Sufficient halogen or hypohalite was added to consume 10–20% of the diene. The reactions were done in the dark, and were maintained near −10° with an ice–alcohol bath. The reactions occurred instantaneously. The yields were based on the amount of hypohalite or halogen that was added.

Stability of the Products.—The stabilities of dibromides **2** and **6** to vpc analysis conditions have been discussed previously.[6] **2** was allowed to stand in each of the solvents at 0° and room temperature for 3 days. Analysis after 3 days showed negligible rearrangements. Reaction products were analyzed immediately after bromination.

Acetoxy bromides **4** and **8** showed no rearrangement after collection from the gas chromatograph. Samples of **4** and **8** at room temperature showed the same composition after 7 weeks. Pure **4** did equilibrate to a mixture of 34% of **4** and 66% of **8** after heating for 1 week at 80°.

Dichlorides **1** and **5** are known to be stable.[17] Acetoxy chlorides **3** and **7** were assumed to be stable, since allylic chlorides and acetates are known to be considerably more stable than their corresponding bromine analogs. Also, **3** and **7** showed no rearrangement during distillation.

(10) E. H. Farmer, C. D. Lawrence, and J. F. Thrope, *J. Chem. Soc.*, 729 (1928).

(11) It is difficult to correlate the effect of solvent change on the 1,2/1,4 ratio with Buckles' observation[9] that the charge becomes localized as the polarity increases, and with an earlier study of ours on the bromination of isoprene [V. L. Heasley, *et al.*, *J. Org. Chem.*, **33**, 2342 (1968)]. Also, the large 1,2/1,4 ratio ion methanol is completely anomalous. We hope that continued investigations in this area may help resolve these problems.[5b]

(12) There is considerable confusion in the textbooks concerning this reaction. One author does not consider the effect of solvent and indicates that the 1,2 isomer is essentially the *only* product; another author states that the 1,4 isomer is the predominant product in this reaction; and a third author states correctly that under kinetic control the 1,2 isomer is the predominant product only in nonpolar solvents.

(13) J. C. Evans, G. Y. S. Lo, and Y. L. Chang, *Spectrochim. Acta*, **21**, 973 (1965).

(14) H. Haubenstock and C. A. VanderWerf, *J. Org. Chem.*, **29**, 2993 (1964).

(15) "Dictionary of Organic Compounds," Vol. II, 4th ed, Oxford University Press, New York, N. Y., 1965, p 965.

(16) We have shown previously[4a] that bromination of butadiene occurs by an ionic mechanism at a mole fraction of 0.05 or less. Previous attempts to cause acetyl hypobromite to add by a radical mechanism to 1-hexene failed under all conditions. [See V. L. Heasley, *et al.*, *Tetrahedron Lett.* 1573 (1970)]. Similarly, we have recently found that acetyl hypochlorite added ionicly to 1-hexene even in neat 1-hexene.

(17) B. R. Brooks, "The Chemistry of the Nonbenzeneoid Hydrocarbons," Reinhold, New York, N. Y., 1940, p 365.

Analysis Conditions.—The vpc analyses of the products were accomplished with an Aerograph 90 P-3 gas chromatograph and an F & M 700 chromatograph. Dichlorides **1** and **5** and acetoxy chlorides **3** and **7** were analyzed on a 7 ft × 0.25 in. column packed with 1.5% dinonyl phthalate on 60–80 mesh DMCS Chromosorb W. The column used for analyses of dibromides **2** and **6** and acetoxy bromides **4** and **8** had a length of 4 ft and was packed identically with the above column. The internal standards for the chlorine systems and bromine sytems were, respectively, *p*-dichlorobenzene and *p*-chlorobromobenzene. Other pertinent data on the analyses are summarized in Table V. It was necessary to separate 1,4-dichloro-2-butene (**5**) and 3-acetoxy-4-chloro-1-butene (**3**) under the following conditions: column dimensions, 7 ft × 0.125 in.; flow rate (He), 60 ml/min; temperature, 40°; column composition, 2.5% SE-30 on 80–100 mesh DMCS Chromosorb W.

TABLE V

VPC DATA ON THE ANALYSES OF THE DIHALIDES AND ACETOXY HALIDES

Compd	Column temp, °C	Retention time, min[a]	Wt/area constant[b]
1	50	2.7	0.95
5	50	8.9	0.92
Std	50	13.05	
3	70	5.2	0.75
7	70	18.2	1.1
Std	70	7.7	
2	60	5.2	1.3
6	60	22.3	1.2
Std	60	16.9	
4	71	4.6	1.0
8	71	16.7	1.3
Std	71	7.5	

[a] The flow rate (He) was 60 ml/min, except for the acetoxy chlorides **3** and **7** for which it was 75 ml/min. [b] The wt/area constants were computed from the following formula: wt of compd/wt of std ÷ area of compd/area of std equals the constant.

Concerning the Yields.—The chlorination of butadiene was carried to approximately 10% completion in order to avoid chlorination of the products; no change in product composition or yield was observed when the reaction was carried to 5% completion. We conclude that reaction of the chloronium ion with butadiene may be responsible for lowering the yield in all of the solvents except acetonitrile or nitromethane. In the case of acetonitrile solvent incorporation was undoubtedly the principal reaction, as was mentioned earlier in this paper. In nitromethane, unidentified products were formed which crystallized out.

We carried out an experiment to determine whether the lower yields in the addition of the hypohalites to butadiene might be caused by further reaction with the products (3,4- and 1,4-acetoxy halides). A solution of acetoxy bromides **4** and **8**, butadiene, and solvent was prepared to correspond to an actual reaction mixture. To this mixture was added acetyl hypochlorite. Subsequent analysis showed no changes in the concentrations of **4** or **8**. Since acetyl hypochlorite does not add to **4** or **8** in the presence of excess butadiene, under identical conditions it should not react with **3** or **7**, and acetyl hypobromite should not react with **4** or **8**.

The yields in the addition of acetyl hypobromite are based on the amount of hypobromite added, and in turn, the concentration of the hypobromite solution was determined by iodometric titration. It is possible that there are compounds in the acetyl hypobromite solution which react with iodide to give iodine, but do not add to butadiene to give **4** or **8**. This would lead to lower yields.

We have determined that in certain solvents butadiene catalyzes decomposition[18] of the acetyl hypochlorite to CO_2. Acetyl hypochlorite was added to butadiene in several solvents and the CO_2 was trapped in $Ba(OH)_2$. The percentages of the hypochlorite which was converted to CO_2 follow: dichloromethane (20%), *n*-pentane (40%), and nitromethane (9%).

We looked for substitution in the chlorination in dichloromethane and *n*-pentane, and found none. In the case of acetyl hypochlorite, substitution (acetic acid formation) was absent in all of the solvent except acetonitrile, in which it was approximately 30%. Acetyl hypobromite gave no appreciable elimination in any of the solvents.

Registry No.—**1**, 760-23-6; **2**, 10463-48-6; **3**, 13422-63-4; **4**, 34414-26-1; **5**, 110-57-6; **6**, 821-06-7; **7**, 34414-28-3; **8**, 33746-94-0; Cl_2, 7782-50-5; Br_2, 7726-95-6; ClOAc 758-11-2; BrOAc 4254-22-2; butadiene, 106-99-0.

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(18) We assume that methyl chloride was also formed in this reaction in a type of "Hunsdiecker reaction."

A Search for the Addition of Monodentate Nucleophiles to Boric and Benzeneboronic Acids in Water[1]

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A spectrophotometric search for the addition of a variety of monodentate oxygen, nitrogen, sulfur, and carbon nucleophiles to boric and benzeneboronic acids in aqueous solution was made. None of the nucleophiles appeared to react significantly with boric acid. Among the nucleophiles which were tested with benzeneboronic acid, only 1-methylimidazole, imidazole, hydrazine, and probably 2,2,2-trifluoroethoxide ion reacted. The equilibrium constant for the addition of trifluoroethoxide ion to benzeneboronic acid was estimated to be 3500 M^{-1}, at 25° and 1 M ionic strength. The equilibrium constants for the addition of 1-methylimidazole and imidazole were determined spectrophotometrically and, in one case, potentiometrically and have values of 12.2 and 10.7 M^{-1}, respectively, at 25° and 1 M ionic strength. Apparent acid dissociation constants for boric and benzeneboronic acids in the presence of some salts and organic solutes are reported.

Boric acid and boronic acids exist in water as trigonal compounds which ionize by the addition of hydroxide ion to form tetrahedral compounds (eq 1, $XR' = OH^-$).[2,3] The addition of monodentate nucleophiles other than hydroxide ion to boric and boronic acids in water has received little attention. Edwards has described the reaction of hydroperoxide anion with boric acid (eq 1, $XR' = OOH^-$) and determined an approximate equilibrium constant for the reaction.[4] Tanner and Bruice have reported that phenols do not form esters with aqueous boric acid in appreciable amounts; however, they do not give the experimental data upon which this conclusion is founded.[5] In this paper we describe a search for the addition of a variety of monodentate ligands to boric acid and benzeneboronic acid in water. Benzeneboronic acid was found to react with 1-methylimidazole, imidazole, hydrazine, and probably 2,2,2-trifluoroethoxide anion. Except for the reaction with hydrazine, the equilibrium constants for these reactions have been determined. In other cases which we investigated no significant reaction was detected, and therefore we report only upper limits for the equilibrium constants.

$$RB(OH)_2 + XR' \rightleftharpoons RB(OH)_2XR' \qquad (1)$$

Experimental Section

Materials.—Reagent grade boric acid and potassium tetraborate were used without further purification. Benzeneboronic acid from Aldrich Chemical Co. was recrystallized twice from water; it gave the theoretical equivalent weight upon titration with sodium hydroxide in the presence of 0.5 M mannitol.[6] The nucleophiles which were used, with the exceptions of p-nitrobenzenethiol, phenol, aniline, and nitromethane, were either recrystallized or redistilled.

Methods.—Spectra were recorded with a Unicam SP800A recording spectrophotometer; individual absorbance readings were taken with either the Unicam or a Gilford 240 spectrophotometer. Teflon-stoppered, 1-cm cuvettes were generally used; in a few cases 5 mm or 1 mm cuvettes were used. pH values were measured with a Radiometer 25 SE pH meter. The meter was standardized just before use with standard buffers at two pH values which encompassed the range of pH measurements. All solutions which were used in the potentiometric determinations of the association constants (see Table II) were prepared with degassed and deionized water saturated with nitrogen and were kept under argon during the measurement of pH. Also, the buffers of benzeneboronic acid which were used for this purpose were made from the acid with carbonate-free potassium hydroxide.[7]

All experiments were carried out with reaction mixtures at 25.0 ± 0.1° and at ionic strength 1.0 M, adjusted with KCl.

Results and Discussion

pK Values of Boric and Benzeneboronic Acids.—Table I presents our values and ones from the literature for the apparent pK's of boric and benzeneboronic acids. The values increase upon the addition of solutes

TABLE I

APPARENT pK VALUES OF BORIC AND BENZENEBORONIC ACIDS, AT 25° AND 1 M IONIC STRENGTH

Boron compd	M	Solvent	pK_{BH}
Boric acid	0.004	Water	9.02[a]
		Water	9.18[b]
	0.004	0.30 M p-Dioxane	9.05[a]
	0.004	0.35 M p-Dioxane	9.08[a]
	0.004	0.40 M p-Dioxane	9.08[a]
	0.004	0.53 M p-Dioxane	9.12[a]
	0.004	0.10 M Furan	9.06[a]
		4.3 M Ethanol	9.87[c]
Benzeneboronic acid	0.004	Water	8.68[d]
		Water	8.86[b]
		4.3 M Ethanol	9.70[c]

[a] From potentiometric titrations with 1 N NaOH. The pK was obtained by plotting the data according to the equation pH = pK + log [B]/[HB], where [B] is the concentration of the basic species and [HB] is the concentration of the acid species. In each case a mixture which was identical except for the absence of the boron compound was also titrated with 1 N NaOH. The values of [B] were obtained by subtracting the milliliters of base required to achieve a pH in this control from the milliliters of base required to achieve the same pH in the titration mixture. The values of [HB] were calculated by subtracting the values of [B] at each pH from the end point value of [B]. The plots of pH *vs.* log [B]/[HB] were linear with slopes of 0.93–1.1. [b] In water, at 25° and 0.04 M ionic strength or less, from ref 6. [c] In 4.3 M ethanol, at 25° and 0.04 M ionic strength or less, from reference given in footnote *b*. [d] From a spectrophotometric titration at 267 nm, where the molar extinction coefficients of the acidic and basic species are 435 and 125 M^{-1} cm^{-1}, respectively. For the procedure, see V. Gold, "pH Measurements," Methuen, London, 1956, Chapter VIII. The solutions were buffered at each pH by the benzeneboronic acid itself.

(1) (a) Supported by Grants GB12848 and GB29205 from the National Science Foundation, a fellowship to K. A. K. from the National Institutes of Health training grant to the Department of Biochemistry and Molecular Biology, and a fellowship to R. C. J. from the National Science Foundation. (b) Address inquiries to G. E. L.

(2) R. P. Bell, J. O. Edwards, and R. B. Jones in "The Chemistry of Boron and Its Compounds," E. L. Muetterties, Ed., Wiley, New York, N. Y., 1967, Chapter 4.

(3) J. P. Lorand and J. O. Edwards, *J. Org. Chem.*, **24**, 769 (1959).

(4) J. O. Edwards, *J. Amer. Chem. Soc.*, **75**, 6154 (1953).

(5) D. W. Tanner and T. C. Bruice, *ibid.*, **89**, 6954 (1967).

(6) G. E. K. Branch, D. L. Yabroff, and B. Bettman, *ibid.*, **56**, 937 (1934).

(7) C. W. Davies and G. H. Nancollas, *Nature (London)*, **165**, 237 (1950).

less polar than water. This increase can be explained by the fact that the ionization reaction, $RB(OH)_2 \rightleftharpoons RB(OH)_3^- + H_3O^+$, is one in which a neutral species yields two ions. An additional complication in the case of ethanol is that ethanol can react with the acids to form an ester (eq 2, R'XH = CH_3CH_2OH). Because

$$RB(OH)_2 + R'XH \rightleftharpoons RB(OH)XR' + H_2O \quad (2)$$

the pK values of ethanol and water are about the same,[8] it seems likely that the equilibrium constant for this reaction *as written* is close to one. The qualitative observation that esters of boric acid hydrolyze in water supports this view.[9] Also, the analogous equilibrium constant for the esterification of acetic acid has a value of 3.3 at 25°.[10] The fraction as ester in 4.3 M ethanol therefore probably lies in the 0 to 0.5 range. If the ester has a much higher pK than the acid, its formation alone could account for the rise in pK in ethanol. However, the substitution of OC_2H_5 for OH probably does not alter the pK value by more than 0.3 units, so that the increase in the apparent pK values which is caused by ethanol is probably largely a solvent effect.

Reaction of Benzeneboronic Acid with Trifluoroethanol.—Solutions of pH 8.60 that contained 0.005 M benzeneboronic acid at 1 M ionic strength in water, in 1 M ethanol, and in 1 M 2,2,2-trifluoroethanol were prepared by determining how much NaOH was necessary to adjust trial solutions of the acid to this pH. The absorbances of these solutions at 267 nm, which is the wavelength of maximum absorbance for the acid itself, against blanks which lacked the benzeneboronic acid were 1.465, 1.626, and 1.359, respectively. The ultraviolet spectra were identical in shape. A similar experiment in which the spectra were obtained in water, 2 M ethanol, and 2 M trifluoroethanol, gave a qualitatively similar result and showed that the absorbances did not change over a period of 18 hr. On the other hand, the spectrum of benzeneboronic acid was not altered by 1 M ethanol or trifluoroethanol at pH 2 and 1 M ionic strength. For the reasons discussed above, the most likely explanation of the result with ethanol is that the ethanol increased the apparent pK of benzeneboronic acid by a solvent effect.[11] The molar absorbancies of the benzeneboronic acid and anion at 267 nm in water (ϵ_{HB} and ϵ_B) were determined to be 435 and 125 M^{-1} cm^{-1}, respectively, and therefore the concentrations of acid and base present in the 1 M ethanol were 0.00322 and 0.00178 M and the apparent pK is 8.86.

The result with trifluoroethanol cannot be interpreted unambiguously, since both the solvent effect and the tendency of trifluoroethanol to react with benzeneboronic acid contribute to the result. In order to estimate a value for the equilibrium constant for the addition of trifluoroethoxide anion to benzeneboronic acid (eq 1, R'X = $CF_3CH_2O^-$), we will assume that the solvent effect is the same as that with ethanol and that the equilibrium constant for the esterification reaction (eq 2, R'XH = CF_3CH_2OH) is close to unity. This latter assumption means that the fraction as the ester $CF_3CH_2OBC_6H_5(OH)$ is less than about 5%. According to these assumptions, the smaller absorbance in the presence of 1 M trifluoroethanol than in the presence of 1 M ethanol is due to the formation of the species $CF_3CH_2OB^-C_6H_5(OH)_2$, which would be expected to have a molar absorbancy similar to that of benzeneboronate anion. The approximate concentration of this species is given by eq 3, where A_E and A_{TFE} are the absorbances

$$A_E - A_{TFE} = \left[\epsilon_{BH}\frac{a_H}{a_H + K_{BH}} + \epsilon_B\frac{K_{BH}}{a_H + K_{BH}} - \epsilon_B\right] \times [RB(OH)_2XR'] \quad (3)$$

of the reaction mixtures with ethanol and trifluoroethanol, a_H is the activity of the hydrogen ion, and K_{BH} is the acid dissociation constant of benzeneboronic acid in 1 M ethanol. Using this concentration, we can calculate an approximate equilibrium constant for the formation of the trifluoroethoxide adduct, according to eq 4, where the subscript T signifies the total concentration of all species and $K_{R'XH}$ is the acid dissociation constant of trifluoroethanol (4×10^{-13} at 25°[8]). The estimated value for K_N is 3500 M^{-1}.

$$K_N = \frac{[RB(OH)_2XR']}{[RB(OH)_2][XR']} = \frac{[RB(OH)_2XR']}{([RB(OH)_2]_T - [RB(OH)_2XR']) \times (a_H/K_{BH} + a_H)[R'XH]_T(K_{R'XH}/K_{R'XH} + a_H)} \quad (4)$$

The equilibrium constant for the corresponding reaction with hydroxide ion (eq 1, R'X = HO^-) is equal to K_{BH}/K_W, where K_W is the ion product of water; and therefore it has a value of about 1.4×10^5 M^{-1}. Thus, it appears that the difference in basicity of 3.3 log units between hydroxide ion (the pK of water is 15.7) and trifluoroethoxide ion is associated with a difference in log K_N of only 1.6 log units. This greater sensitivity of basicity to electronic effects means that the proton is more electron demanding than the $RB(OH)_2$ group. This conclusion is the one that is expected from the fact that the boron adduct bears a net negative charge.

Reaction of Benzeneboronic Acid with 1-Methylimidazole and with Imidazole.—The addition of 1-methylimidazole buffers or imidazole buffers to solutions of benzeneboronic acid at the same pH as the buffer caused the spectrum of the benzeneboronic acid to change from predominantly the spectrum of the acidic species to one which resembled that of the benzeneboronate anion. The spectral change was complete within less than 15 sec, and the new spectrum was stable for at least 2 hr.

The apparent equilibrium constants for these reactions were determined spectrophotometrically at several pH values. The absorbances at 267 nm of reaction mixtures which contained a single concentration of benzeneboronic acid in the presence of various concentrations of 1-methylimidazole or imidazole buffer were measured against air and then corrected for the absorbance of the buffer by subtracting the absorbances of blank mixtures which lacked benzeneboronic acid and which were also measured against air. The concentrations of both the acidic and basic species of the buffer were five times or more as large as the concentration of the benzeneboronic acid. Under these

(8) P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, **82**, 795 (1960).

(9) A. Scattergood, W. H. Miller, and J. Gammon, Jr., *ibid.*, **67**, 2150 (1945).

(10) W. P. Jencks and M. Gilchrist, *ibid.*, **86**, 4651 (1964).

(11) The effects of ethanol and trifluoroethanol upon the spectrum are probably not due to solvent effects upon the glass electrode, since the pH value of 10^{-3} N HCl in water, 1 M ethanol, and 1 M trifluoroethanol at 25° and 1 M ionic strength were found to be 3.06, 3.08, and 3.09, respectively.

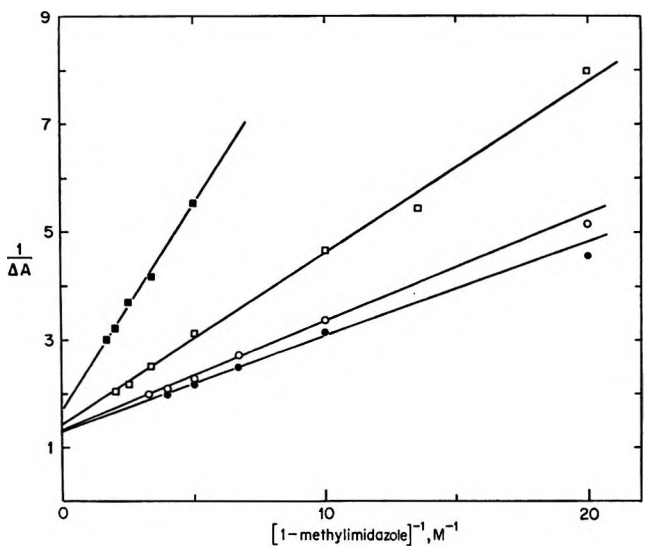


Figure 1.—Spectrophotometric determination of the equilibrium constant for the reaction between 1-methylimidazole and benzeneboronic acid, at 25° and 1 M ionic strength. The reciprocal of the difference between the absorbance of benzeneboronic acid alone and the absorbance of benzeneboronic acid in the presence of 1-methylimidazole buffers, at 267 nm, is plotted against the reciprocal of total concentration of 1-methylimidazole buffer. The concentration of benzeneboronic acid was 0.0030 M throughout. The 1-methylimidazole buffers contained 20 (■), 40 (□), 60 (○), and 80% (●) free base.

conditions, the equation which describes the formation of a 1:1 complex is eq 5, where ΔA is the difference be-

$$\frac{1}{\Delta A} = \left(\frac{1}{K_{obsd}[RB(OH)_2]_T\Delta\epsilon}\right)\left(\frac{1}{[R'XH]_T}\right) + \frac{1}{[RB(OH)_2]_T\Delta\epsilon} \quad (5)$$

tween the absorbance of the benzeneboronic acid alone at the pH of the buffer and the absorbance of the mixture of benzeneboronic acid and 1-methylimidazole or imidazole buffer; K_{obsd} is the apparent equilibrium constant for complex formation; $[RB(OH)_2]_T$ is the total concentration of benzeneboronic acid; $\Delta\epsilon$ is the difference between the sum of the molar extinction coefficients of the benzeneboronic acid $[(\epsilon_{BH}a_H + \epsilon_B K_{BH})/(K_{BH} + a_H)]$ and the 1-methylimidazole or imidazole buffer ($\epsilon_{R'XH}$) and the extinction coefficient of the complex (ϵ_c); and $[R'XH]_T$ is the total concentration of the 1-methylimidazole or imidazole buffer. Linear plots of $1/\Delta A$ *vs.* $1/[R'XH]_T$ were obtained in all cases (see Figure 1 for the results with 1-methylimidazole); and thus the data are adequately explained by the assumption of a 1:1 complex. The values of K_{obsd} increased with the fraction of base in the buffer. This fact suggested that the complex contains the elements of 1-methylimidazole or imidazole base and the acidic species of benzeneboronic acid. The values of the pH-independent equilibrium constant for the formation of the complex from these species (K_N) were obtained by use of eq 6, where $K_{R'XH}$ is the acid dissociation con-

$$K_N = K_{obsd}\left(\frac{K_{BH} + a_H}{a_H}\right)\left(\frac{K_{R'XH} + a_H}{K_{R'XH}}\right) \quad (6)$$

stant of 1-methylimidazolium ion (4.6×10^{-8} M) or imidazolium ion (6.0×10^{-8} M). The values of K_N which were calculated from the various values of K_{obsd} were the same within ±5% of the average value and equal to 12.2 M^{-1} for the complex with 1-methylimidazole and 10.7 M^{-1} for the complex with imidazole.

The equilibrium constant for the reaction of 1-methylimidazole with benzeneboronic acid was also determined by a potentiometric method. Since 1-methylimidazole complexes detectably only with the acidic form of benzeneboronic acid, the addition of 1-methylimidazole base to a buffer of benzeneboronic acid should remove the acidic species and therefore raise the pH to a higher value than the value which would be reached in the absence of complexation. The equilibria which must be considered are given in eq 7,

$$\begin{array}{ccc} R'X + RB(OH)_2 & \overset{K_N}{\rightleftharpoons} & \text{Complex} \\ K_{R'XH}\uparrow\downarrow & & \uparrow\downarrow K_{BH} \\ R'XH & & \bar{R}B(OH)_3 \end{array} \quad (7)$$

where R'XH and R'X refer to the acidic and basic species of the tertiary amine. This scheme yields eq 8,

$$K_N = \frac{K_{BH}K_{R'XH}[RB(OH)_2]_0}{[R'X]a_B[R\bar{B}(OH)_3]_0K_{R'XH} + [R'X]^2a_H^2} - \frac{K_{BH}}{[R\bar{B}(OH)_3]_0K_{R'XH} + [R'X]a_H} - \frac{1}{[R'X]} \quad (8)$$

in which $[RB(OH)_2]_0$ and $[RB^-(OH)_3]_0$ are the concentrations of these species in the absence of 1-methylimidazole. Solution of eq 8 for K_N requires the value of [R'X], the concentration of the basic species. In our experiments (see Table II) we used total con-

Table II
Equilibrium Constants for the Reaction of Tertiary Amines with Benzeneboronic Acid, from Potentiometric Measurements at 25° and 1 M Ionic Strength

Amine	M of $RB(OH)_2$ buffer	pH of buffer alone	M of amine[a]	pH of buffer + amine	K_N[b]
1-Methylimidazole	0.01	9.16	0.15	9.72	11.0
	0.02	9.17	0.30	9.89	10.3
	0.01	8.68	0.15	9.37	11.2
	0.02	8.69	0.30	9.51	11.3
	0.02	9.16	0.30	9.91	11.6
	0.023	9.18	0.345	9.96	11.1
	0.01	9.16	0.15	9.72	11.0
Pyridine	0.01	9.15	0.15	9.25	1.6
	0.02	9.16	0.30	9.35	1.8
	0.01	8.69	0.15	8.80	1.6
	0.02	8.70	0.30	8.89	1.9

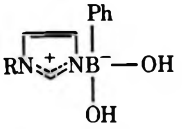
[a] Total concentration of all species. [b] K_N is the equilibrium constant for formation of the complex from the tertiary amine base and the acidic species of the boron compound. The values of K_N were calculated from eq 8 in the text; the values of K_{BH} in water at 25° and 1 M ionic strength were taken from Table I; the values of $[RB(OH)_2]_0$ and $[R\bar{B}(OH)_3]_0$ were calculated from the pH of the buffer in the absence of amine and the total concentration of buffer by use of the equation in footnote a of Table I; the value of $pK_{R'XH}$ for 1-methylimidazolium was determined to be 7.34 at 25° and 1 M ionic strength by potentiometric titration; and the value of $pK_{R'XH}$ for pyridinium at 25° and 1 M ionic strength with KCl is 5.52, according to W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, 90, 2622 (1968).

centrations of 1-methylimidazole which were 15 times those of the benzeneboronic acid. Under these conditions, even if all the boronic acid were complexed with 1-methylimidazole, the concentration of the free base would be equal to 92% or more of the total concentration of 1-methylimidazole. Consequently, we have calculated values of K_N from eq 8 by using the total

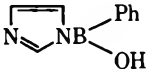
concentrations of 1-methylimidazole in place of [R′X]. Sample calculations in which we have assumed various possible values for [R′X] show that this approximation does not change the values of K_N for any of the cases given in Table II, including that of benzeneboronic acid plus pyridine, by more than 15%. The values of K_N for the reaction of 1-methylimidazole with benzeneboronic acid which have been obtained by the potentiometric method in this way are the same over a range of buffer ratios and 1-methylimidazole concentrations and agree well with the value from the spectrophotometric method (Table II).

The potentiometric method was also used to search for complex formation between benzeneboronic acid and pyridine (Table II). Small increases in pH occurred when pyridine was added to buffers of benzeneboronic acid. Since these increases may be partly due to other factors, such as a solvent effect upon pK_{HB} (see Table I), the small value for K_N is probably best considered only an upper limit. No complex formation with pyridine was detected spectrophotometrically (see below).

On the basis of the above evidence the most likely structures for the complexes between benzeneboronic acid and 1-methylimidazole or imidazole is **1**. *A priori*, an alternate possible structure for the complex with imidazole was **2**, the product of the dehydration of **1**. However, the fact that the equilibrium constant for the formation of the complex with imidazole is virtually the same as that for the formation of the complex with 1-methylimidazole and the fact that the ultraviolet spectra of the two complexes are the same shows that **2** is not formed in significant amounts. Philipp and Bender have reported B^{11} nmr evidence for the formation of a complex between imidazole and dimethyl *m*-nitrobenzeneboronate in methanol.[12]



1, R = CH_3 or H



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Search for Other Reactions.—On the basis of the known chemistry of boron compounds,[13-15] we expect that the following equilibria between oxygen, sulfur, and carbon nucleophiles and boric or benzeneboronic acids are rapidly established in water.

$$\begin{array}{ccc} R'X^- + RB(OH)_2^- & \overset{K_N}{\rightleftharpoons} & R'X\bar{B}(OH)_2R \\ K_{R'XH}\Big\downarrow\Big\uparrow \pm H^+ & & \Big\downarrow\Big\uparrow \pm H^+ \\ R'XH + RB(OH)_2 & \overset{K_E}{\rightleftharpoons} & R'X\bar{B}(OH)R + H_2O \end{array} \qquad (9)$$

X = O, S, C

The expected equilibria for primary and secondary amines are somewhat more complicated.

$$\begin{array}{ccc} & & R_2'N\bar{B}(OH)_2R \\ & & \Big\downarrow\Big\uparrow \pm H^+ \\ R_2'NH + RB(OH)_2 & \overset{K_E}{\rightleftharpoons} & R_2'NB(OH)R + H_2O \\ & & \Big\downarrow\Big\uparrow \\ R_2'NH + RB(OH)_2 & \overset{K_N}{\rightleftharpoons} & R_2'\overset{+}{H}N\bar{B}(OH)_2R \\ K_{R'XH}\Big\downarrow\Big\uparrow \pm H^+ & & \Big\downarrow\Big\uparrow \pm H^+ \\ R_2'\overset{+}{N}H_2 + RB(OH)_2 & \overset{K_X}{\rightleftharpoons} & R_2'\overset{+}{H}N\bar{B}(OH)R + H_2O \end{array} \qquad (10)$$

In the case of tertiary amines, only the equilibria in eq 10 with constants K_N and K_X are possible.

A spectrophotometric search for these reactions was undertaken. The spectra of a number of nucleophiles which absorb strongly in the visible or ultraviolet region were determined at one pH value in the presence and absence of a great excess of boric acid, which itself shows only low end absorption (ϵ_{230} is less than 0.20 M^{-1} cm^{-1} for potassium borate buffer, 60% base) (Table III). Also, the spectrum of benzeneboronic acid alone was compared with its spectrum at the same pH value in the presence of an excess of each of several nucleophiles, after subtraction of the spectrum of the nucleophile alone (Table III). With the exception of the case of hydrazine and benzeneboronic acid at pH 8.35, the spectrum of the absorbing compound in each case was not altered significantly by the reagent in excess during the period of time given in Table III. In the presence of hydrazine buffer at pH 8.35 the spectrum of benzeneboronic acid shows λ_{max} 265 nm, ϵ 370 M^{-1} cm^{-1}, which is similar to that of benzeneboronic acid alone, but the spectrum lacks the weaker maxima at 259 and 272 nm which benzeneboronic acid alone shows and the molar absorbancy in the 265–300 nm range is greater. This difference may be due to the formation of the $H_2NNHB(OH)Ph$ species;[16] however, we have not investigated this reaction in detail.

Table III includes estimates of the upper limits for the values of K_N (see eq 9 and 10). These estimates were made by assuming that the spectrum of the tetrahedral adducts would be the same as that of the acidic species of the nucleophile in the case of the search for reactions with boric acid and the same as that of the benzeneboronate anion in the case of the search for reactions with benzeneboronic acid.

Upper limits for the equilibrium constants for the formation of the trigonal species, R′XB(OH)R and $R_2'HN^+B(OH)R$ (eq 9 and 10), cannot be estimated from the spectra in acidic solution because we cannot estimate the spectral changes which would accompany the formation of these boron compounds. Although it seems likely that the spectra of these boron compounds would differ somewhat from those of the reactants, the absence of spectral changes is not definitive evidence for no reaction. It is worth noting that the absence of spectral changes with the absorbing nucleophiles and boric acid buffers at alkaline pH shows that significant amounts of the trigonal species R′XB(OH)R and $R_2'HN^+B(OH)R$ have not formed under these conditions,

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(16) M. S. Bains, *Can. J. Chem.*, **44**, 534 (1966).

TABLE III

SPECTROPHOTOMETRIC SEARCH FOR REACTIONS BETWEEN NUCLEOPHILES AND BORIC OR BENZENEBORONIC ACID, IN WATER AT 25° AND 1.0 *M* IONIC STRENGTH

Registry no.	Nucleophile	pK[a]	Concn, *M*	Boron compd, *M*	pH[b]	Time[c] interval, hr	K_N[d] M^{-1}
			Boric Acid				
62-53-3	Aniline	4.58	10^{-3}	1.0	9.4	12	0.15
			4.6×10^{-3}	0.32	1.0	12	
108-95-2	Phenol	9.95	3.6×10^{-4}	1.0	9.50	12	0.8[e]
			9.1×10^{-4}	0.28	1.0	12	
100-02-7	*p*-Nitrophenol	7.14	7×10^{-5}	0.30	9.13	24	0.5
			7×10^{-5}	0.20	0.7	45	
108-98-5	Benzenethiol	6.5	1.5×10^{-5}	0.30	9.1	1	5.5
			1.5×10^{-5}	0.20	0.7	0.25	
1849-36-1	*p*-Nitrobenzenethiol	5.1	2.0×10^{-4}	0.30	9.1	1	0.7
10494-75-4	2-Methoxyethanethiol	9.5	4×10^{-4}	1.0	9.5	0.05[f]	0.4
75-52-5	Nitromethane	10.3	1.2×10^{-3}	0.50	10.0	0.5[g]	10
			Benzeneboronic Acid				
109-85-3	2-Methoxyethylamine	9.2	1.0	5.0×10^{-3}	9.08		5
			1.0	5.0×10^{-3}	8.68	22	4[h]
			0.90	3.0×10^{-3}	1.0		
280-57-9	Triethylenediamine	2.9, 8.8	0.80	3.0×10^{-3}	8.49		2.2
			0.80	1.8×10^{-3}	5.2		0.3
302-01-2	Hydrazine	8.1	0.50	3.0×10^{-3}	8.35		*i*
			0.50	3.0×10^{-3}	1.3		0.25
110-91-8	Morpholine	8.3	0.70	3.0×10^{-3}	8.58		2.0
			0.70	3.0×10^{-3}	1.0		
583-58-4	3,4-Lutidine	6.5	0.052	0.0158	7.62		1.6[j]
110-86-1	Pyridine	5.2	0.08	1.1×10^{-3}	5.2		5
753-90-2	2,2,2-Trifluoroethylamine	5.7	0.4	3.3×10^{-3}	5.7		0.5
57-12-5	Cyanide	9.4	1.0	4.8×10^{-3}	8.60	*k*	1.3
16887-00-6	Chloride		1.0	3.0×10^{-3}	2.7		0.12[l]

[a] Of conjugate acid; from W. P. Jencks in "Handbook of Biochemistry," H. A. Sober, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1968, pp J150–J189. [b] Adjusted with KOH or HCl. [c] Period between preparation of the reaction mixture and the last recording of its spectrum. Where no time is noted, the spectrum was recorded once about 15 min after preparation of the reaction mixture. [d] These values for K_N are upper limits. In the case of the boric acid buffers, they have been calculated by use of the equation

$$K_N = \frac{\Delta A(a_H + K_{R'XH})}{([R'XH]_T \Delta\epsilon - \Delta A)K_{R'XH}/[RB(OH)_2]}$$

where ΔA is the difference between the absorbance of the nucleophile in the absence of boric acid buffer and that in the presence of boric acid buffer, $[R'XH]_T$ is the total concentration of the nucleophile in all species, $\Delta\epsilon$ is the difference between the apparent molar absorbancy of the nucleophile at the pH of the reaction mixture and the molar absorbancy of the acidic species alone, $K_{R'XH}$ is the acid dissociation constant of the nucleophile, and $[RB(OH)_2]$ is the concentration of boric acid, including polymeric species, in the boric acid buffer. In the case of benzeneboronic acid, the upper limits for the values of K_N were calculated in a similar manner by use of eq 3 and 4 in the text, except that the concentration of the basic species of the nucleophile was known from the preparation of the buffer. The calculations were made by taking ΔA as 0.1, usually at the wavelength where $\Delta\epsilon$ is maximal; in fact, ΔA was less than 0.05 except in the cases which are noted. [e] The spectra showed ΔA at 233 nm, where $\Delta\epsilon$ is 2,800 M^{-1} cm^{-1}, to be about 0.10 (1-cm path length). This small ΔA may be due either to a conversion of about 10% of the phenol to a boron adduct or to an increase in the apparent pK of phenol by 0.06 log units. [f] The absorbance of the reaction mixtures with and without borate buffer decreased after this time, probably because of oxidation of the thiol to the disulfide. [g] The spectrum did not change between 20 and 30 min after preparation of the solution. Calculation based upon the rate constants for ionization of nitromethane [R. P. Bell and D. M. Goodall, *Proc. Roy. Soc., Ser. A*, 294, 273 (1966)] shows that about 10 min is sufficient time for equilibration of the acid and anion. [h] ΔA at 267 nm, where the $\Delta\epsilon$ term of eq 3 is 155 M^{-1} cm^{-1}, was 0.12 (1-cm light path). [i] A reaction occurs. See the text. [j] Ionic strength, 0.53 *M*. [k] Cyanide buffer slowly forms a compound which absorbs at 293 nm. For this reason the reaction mixtures which contained cyanide buffer were prepared by using stock solutions of KCN and HCl, and the spectra of such mixtures with and without benzeneboronic acid present were determined at the same time after preparation. [l] The reaction mixture without chloride had an ionic strength of 0.002 *M*.

since such reaction would decrease the total concentration of the free nucleophile and thus decrease the concentration of the basic species and the absorbance at wavelengths where the basic species absorbs strongly. The trigonal species, $R_2'NB(OH)R$, which can form from primary and secondary amines, would also not have been detected if its spectrum were identical with that of $R_2'NH$ or $RB(OH)_2$. Moreover, if a large fraction of the absorbing compound were undetected $R_2'NB(OH)R$, then the values of the upper limits for K_N given in Table III would be incorrect.

Comparisons of Reactivities.—The affinities of imidazole and 1-methylimidazole for benzeneboronic acid are much higher than we would expect on the basis of the data for other nitrogenous bases given in Table III and their affinities for the proton (the pK's of imidazole and 1-methylimidazole are 7.22 and 7.34). Two possible explanations for this unusual affinity are that a positive charge next to tetrahedral boron is unfavorable and delocalization of this charge in the imidazole adducts (see 1) is thus relatively stabilizing and/or that there is a strong electrostatic interaction between the

positively charged imidazolium nucleus and the partially negative phenyl ring in the adducts. In order to decide between these two possibilities, it will be necessary to examine the affinities of a series of nitrogenous bases for an alkylboronic acid.

Finally, it is interesting to note that our results show that the affinities of nitrogen, sulfur, and carbon nucleophiles for trigonal boron are not much greater than that of an oxygen nucleophile of the same basicity. This finding is different from that for a carbonyl carbon, for which nitrogen, sulfur, and carbon nucleophiles have a greater affinity than an oxygen nucleophile of the same basicity.[17] Thus, in this sense trigonal boron is more similar to the proton than to trigonal carbon in its chemistry.

Registry No.—Boric acid, 10043-35-3; benzeneboronic acid, 98-80-6; 1-methylimidazole, 616-47-7.

(17) E. G. Sander and W. P. Jencks, *J. Amer. Chem. Soc.*, **90**, 6154 (1968).

A Direct ^1H and ^{19}F Nuclear Magnetic Resonance Study of Boron Trifluoride Complexes with Acetylacetone, Methoxyacetonitrile, Methoxypropionitrile, Methylacetoacetate, Methylmethoxyacetate, Methoxymethylacetate, 2-Methoxyethylacetate, and Methylpyruvate

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A direct proton and fluorine-19 nuclear magnetic resonance chemical shift and area study of boron trifluoride complexes with acetylacetone, methylacetoacetate, methoxyacetonitrile, methoxypropionitrile, methylmethoxyacetate, methoxymethylacetate, 2-methoxyethylacetate, and methylpyruvate has been completed. In these systems ligand exchange is slow enough below $-50°$ to permit the direct observation of pmr signals for bulk ligand and molecules bound to the boron trifluoride. In the nitrile solutions the ^1H and ^{19}F nmr spectra indicate complete complexing at the methoxy linkage. The most stable complexes in solutions of acetylacetone and methylacetoacetate involve the enol tautomers of these molecules. In the remaining systems, complexing at more than one site in the base is indicated by the ^1H and ^{19}F nmr data. The competition by each oxygen site is influenced by basicity differences, steric hindrance, and resonance.

Studies of boron trihalide complexes with organic bases have been undertaken by several calorimetric[1-4] and spectroscopic[5-11] techniques to ascertain the chemical and structural features of the components which influence these interactions. Recent measurements have demonstrated the utility of the direct nuclear magnetic resonance method as a supplementary tool for these investigations.[12-16] The success of this method is based on the ability to slow ligand exchange, thereby allowing the observation of separate nmr signals for bulk ligand and ligand bound to the boron trihalide. When this observation is possible, quantitative measurements of the chemical shifts induced by complex formation, the stoichiometry of the complex, the ligand interaction site, steric effects, and ligand preference can be made. A correlation of these results with those obtained by other techniques frequently is possible.

The present study involves a series of ligands which contain more than one possible interaction site, an oxygen atom in most cases. It was hoped that a measure of competitive complex formation would be possible with several of these molecules. If so, the influence of properties such as molecular complexity, the relative basic strengths of the functional groups present, tautomerism, and molecular resonance structures could be ascertained.

Experimental Section

Methods.—All organic chemicals were of the highest commercial grade available, and they were distilled before use. The boron trifluoride was fractionated at $-110°$. The samples were prepared *in vacuo* and the nmr tube was sealed and stored in liquid nitrogen until the spectrum could be recorded. Each sample contained a few per cent by volume of tetramethylsilane (TMS) and hexafluorobenzene for use as internal nmr chemical shift standards for ^1H and ^{19}F nuclei, respectively.

The chemical shift and area measurements were made with a Varian HA-100 spectrometer, operating at 94.1 MHz for the ^{19}F experiments. With each sample, the nmr measurements for each nucleus were repeated at least a day later to ensure that decomposition had not occurred. This was not a problem with any system reported here. The procedure has been described in more detail in previous publications and it involves observing the nmr spectrum as the sample is cooled in the spectrometer probe.[12-16] In most of the systems studied, exchange was slow enough only at temperatures below $-50°$ to permit the observation of separate bulk and bound ligand signals.

Results.—A summary of all pmr chemical shift and integration data is presented in Table I. As mentioned in the table, the concentrations in all cases were maintained at mole ratios of 1:3:60, BF_3 to base to dichloromethane. Such dilutions were used to avoid intermolecular interactions between ligand molecules. Thus, the chemical shift separations between bound and bulk ligand molecules, represented by the quantity $\Delta\nu(C - B)$ in Table I, are an accurate measure of the effect of complex formation by BF_3 with these bases.

(1) H. C. Brown and R. R. Holmes, *J. Amer. Chem. Soc.*, **78**, 2173 (1956).
(2) T. D. Coyle and F. G. A. Stone, *ibid.*, **83**, 4138 (1961).
(3) M. F. Lappert and J. K. Smith, *J. Chem. Soc.*, 7102 (1965).
(4) N. N. Greenwood and T. S. Srivastava, *J. Chem. Soc. A*, 267, 270 (1965).
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(12) A. Fratiello, T. P. Onak, and R. E. Schuster, *J. Amer. Chem. Soc.*, **90**, 1194 (1968).
(13) A. Fratiello and R. E. Schuster, *Inorg. Chem.*, **7**, 1581 (1968).
(14) A. Fratiello and R. E. Schuster, *Org. Magn. Resonance*, **1**, 139 (1969).
(15) A. Fratiello and R. E. Schuster, *Inorg. Chem.*, **8**, 480 (1969).
(16) A. Fratiello, R. E. Schuster, and M. Geisel, *ibid.*, **11**, 11 (1972).

TABLE I

PROTON CHEMICAL SHIFT AND COORDINATION DATA FOR BORON TRIFLUORIDE COMPLEXES WITH ORGANIC BASES

Base[a]	Temp, °C	Δν(C − B), Hz				BF₃ Fraction Complexed			
		CH_3C	CH_3O	CH_2C	CH_2O	C=O	COC	C≡N	COH
$(CH_3)_2O$	−100		62				1.0		
$(CH_3)_2CO$	−95	65				1.0			
$CH_3CO_2CH_3$	−90	53	52			1.0			
CH_3OH[b]	−100		17						1.1
CH_3CN	−85	Not separated							
$CH_3OCH_2CH_2CH_2CH_3$	−85	6	53	Overlap	84		1.0		
$(CH_3CH_2CH_2CH_2)_2O$	−50	6		Overlap	78		1.1		
$CH_3COC_6H_4OH$[c] 2-Hydroxyacetophenone	−50	27							1.1
$CH_3COCH_2COCH_3$ Acetylacetone	−90	Not separated							
$CH_3COCH_2CO_2CH_3$ Methylacetoacetate	−85	Not separated							
$CH_3OCH_2CO_2CH_3$ Methylmethoxyacetate	−100		42[d]		65	Overlap			
$CH_3CO_2CH_2OCH_3$ Methoxymethylacetate	−100	50	43		Overlap	0.80	0.17		
$CH_3CO_2CH_2CH_2OCH_3$ 2-Methoxyethylacetate	−100	55	67		(2-CH_2) 79 (1-CH_2) 46	0.65	0.44		
	−70					0.41	Broad		
$CH_3COCO_2CH_3$ Methylpyruvate	−100	Not separated							
CH_3OCH_2CN Methoxyacetonitrile	−110	Not separated							
$CH_3OCH_2CH_2CN$ Methoxypropionitrile	−105		65	30	83		1.0		

[a] The solvent in all samples was dichloromethane, and the component mole ratios were 1:3:60, BF_3:base:solvent, within 1–2%. [b] The hydroxyl proton signal was a single line at all temperatures. [c] The hydroxyl proton signal was a single line at all temperatures and the ring proton pattern was too complex to identify bound ligand signals. [d] The 42-Hz separation listed was observed for the methoxy signal. The remaining methyl signal was split about 40 Hz but overlap with the bulk methoxy signal prevented an accurate measure.

Several of the compounds listed in Table I, specifically 2-hydroxyacetophenone and those containing only one oxygen or nitrogen atom, were chosen to provide a chemical shift and integration calibration for both the pmr and ^{19}F nmr measurements. Since several of these species had been studied previously, samples of these reference compounds were prepared in duplicate. All other samples were prepared in triplicate. In every case the chemical shift and area data are the result of two or more measurements with each sample, and they are precise to about 5 (shifts) and 10% (areas), respectively.

It can be seen in Table I that it was not possible to observe bound and bulk signals for all ligands, presumably because exchange is too rapid even at temperatures in the range of −100°. Also, although this observation was possible in the methylmethoxyacetate system, signal overlap prevented an accurate integration. However, as indicated by the data of Table II, the use of ^{19}F nmr as a complementary tool provides another means of determining the structure of these complexes. For example, in the methylmethoxyacetate sample mentioned above, two ^{19}F nmr signals were observed and the separation was large enough to permit an accurate area evaluation.[17]

The nmr chemical shifts listed in Table II were measured with respect to internal C_6F_6, and referred to $CFCl_3$, the usual standard for ^{19}F studies, by the relationship $\delta(C_6F_6) - \delta(CFCl_3) = +162.3$ ppm.[18] The chemical shifts were measured with a precision of at least 0.1 ppm. Since all the BF_3 is bound to a ligand, the area results for those systems exhibiting two or more ^{19}F signals are relative values and they were measured with a precision of at least 5%. The pmr and ^{19}F nmr coordination results were consistent in all cases where a quantitative comparison could be made. Although it was possible to measure signal areas over a much wider temperature range in those systems of multiple ^{19}F peaks, a significant variation was observed only in the 2-methoxyethylacetate system. In some instances, for example the acetylacetone solution, changes in the ^{19}F nmr spectrum with time reflected a slow approach to equilibrium. The results in Table II represent the equilibrium situation in all cases. These examples will be described in detail later.

Discussion

It is evident from the data of Tables I and II that it frequently is possible to observe distinct ^{19}F nmr signals for each BF_3 complex in solution, while only one set of averaged signals is observed in the pmr spectrum of the same sample. This is probably due to factors such as rapid intramolecular proton exchange, small, nonresolvable bulk-bound ligand proton shift differences, and the rate of intermolecular exchange. Since the ^{19}F chemical shift differences are greater than the ^1H values by about a factor of ten, this could determine the upper limit for ligand exchange which can be tolerated. For instance, using the relationship $\tau \simeq 10/2\pi\Delta\nu$ to approximate these rates,[19] a lifetime of about 0.03 sec would be required for the observation of separate ^1H peaks, but only 0.003 sec in the ^{19}F case. These relatively rapid exchange rates are typical of systems involving complex formation at an oxygen atom and it may reflect the strength of these complexes. For example, separate bound and bulk ^1H and ^{19}F nmr signals can be observed at temperatures in the range of 0°, for BF_3 complexes of pyridines and other nitrogen-containing heterocycles.[14-16] These

(17) Typical ^1H and ^{19}F nmr spectra will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C, 20036, by referring to code number JOC-72-2237. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

(18) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," 1st ed, Vol. 2, Pergamon Press, New York, N. Y., 1966, Table 11.26.

(19) H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, **25**, 1228 (1956).

TABLE II

FLUORINE-19 CHEMICAL SHIFT AND COORDINATION DATA FOR BORON TRIFLUORIDE COMPLEXES WITH ORGANIC BASES

Registry no.	Base[a]	Temp, °C	δ, ppm	BF_3 Fraction Complexed
353-42-4	$(CH_3)_2O$	−90	+159.0	1.0
661-27-8	$(CH_3)_2CO$	−85	+148.9	1.0
7611-14-5	$CH_3CO_2CH_3$	−90	+149.8	1.0
373-57-9	CH_3OH	−100	+156.4	1.0
420-16-6	CH_3CN	−85	+144.2	1.0
34804-31-4	$CH_3OCH_2CH_2CH_2CH_3$	−85	+156.0	1.0
593-04-4	$(CH_3CH_2CH_2CH_2)_2O$	−50	+140.8	1.0
34804-32-5	$CH_3COC_6H_4OH$ 2-Hydroxyacetophenone	−50	+133.5	1.0
637-99-0	$CH_3COCH_2COCH_3$ Acetylacetone	−90	+135.9	1.0
34804-34-7	$CH_3COCH_2CO_2CH_3$ Methylacetoacetate	−85	+155.9	0.25
			+150.0	0.17
			+138.3	0.58
34804-35-8	$CH_3OCH_2CO_2CH_3$ Methylmethoxyacetate	−105	+155.8	0.82
			+149.2	0.18
34804-36-9	$CH_3CO_2CH_2OCH_3$ Methoxymethylacetate	−100	+155.0	0.15
			+149.3	0.85
34804-37-0	$CH_3CO_2CH_2CH_2OCH_3$ 2-Methoxyethylacetate	−60	+155.9	0.61
			+149.2	0.39
		−67	+156.0	0.58
			+149.2	0.42
		−76	+156.1	0.55
			+149.3	0.45
		−84	+156.3	0.50
			+149.4	0.50
		−92	+156.4	0.47
			+149.5	0.53
		−100	+156.5	0.43
			+149.6	0.57
		−105	+156.6	0.37
			+149.6	0.63
34804-38-1	$CH_3COCO_2CH_3$ Methylpyruvate	−80	+155.5	0.61
			+150.4	0.24
			+149.1	0.15
34804-39-2	CH_3OCH_2CN Methoxyacetonitrile	−115	+154.6	1.0
34804-40-5	$CH_3OCH_2CH_2CN$ Methoxypropionitrile	−100	+156.1	1.0

[a] The solvent in all samples was dichloromethane, and the component mole ratios were 1:3:60, BF_3:base:solvent, within 1–2%.

heterocycles are much stronger bases than the molecules under study here.

In general the ^1H and ^{19}F nmr data for the eight reference compounds of Tables I and II provide a foundation for reasonable analogies to the remaining compounds of this study. However, even with this series of reference species several interesting features are noticeable. As expected, with only one possible interaction site in a molecule, or in the case of 2-hydroxyacetophenone where the more basic hydroxyl group dominates, simple 1:1 adducts are formed with complexation occurring at the single site. This is verified by the pmr integration data and the observation of only one ^{19}F nmr signal in the spectra of these samples. Only in the acetonitrile system was exchange too rapid to observe the bound ligand signal. Also, pmr signals for methyl groups one or two bonds removed from the interacting oxygen are displaced about 50–60 Hz upon complex formation, with an attenuation to a small displacement of a few hertz if the group is further removed (butyl ethers). The exception is methanol, for which this effect had been noticed and described previously.[12]

The pmr reference data would not have been conclusive in the assignment of interaction sites without the ^{19}F nmr results of Table II. Chemical shifts involving this nucleus are extremely sensitive to the structure of the molecule, even for compounds containing the same functional group. For example, the ^{19}F nmr shift of dimethyl, methyl-*n*-butyl, and *n*-butyl ether appear at progressively lower field, probably the result of steric hindrance. The proton nmr shift displacements are much smaller and, in some cases, similar for different molecules. An excellent illustration of these contrasts is provided by the dimethyl ether and acetone systems, in which the ^1H shift results are practically identical, while the ^{19}F shifts differ by 10 ppm. From the data of Table II, reference ^{19}F chemical shifts for BF_3 complexes at carbonyl (acetone, +149 ppm), carboxyl (methylacetate, +150 ppm), nitrile (acetonitrile, +144 ppm), hydroxyl (2-hydroxyacetophenone, +133 ppm), and ether (methyl-*n*-butyl ether, +156 ppm) functional groups were concluded. In view of the variations of ^{19}F shifts previously noted for the ethers, methyl-*n*-butyl ether was chosen because its structure more closely resembles the methoxy compounds studied. In these cases, a methoxy group was bonded to a fragment containing several carbon atoms. Consequently, similar steric effects should be observed. Similarly, 2-hydroxyacetophenone was chosen as a hydroxyl-group reference compound to provide a more meaningful comparison to the BF_3–enol complexes encountered in this study. In the latter cases (acetylacetone and methylacetoacetate) internal hydrogen bonding is possible with the enol tautomers. This situation also is possible in 2-hydroxyacetophenone, but not with simple alcohols, such as methanol.

From Tables I and II, definitive results were obtained with the BF_3 complexes of methoxyacetonitrile and methoxypropionitrile. Although separate bound and bulk pmr signals were observed only in the latter case, as seen in Figure 1,[17] the large CH_3 and CH_2 shift displacements indicate complexing at the methoxy site. Also, in this system, the pmr integration result of 1.0 reflected total complexing within experimental error at this site. Further, the one ^{19}F signal observed in each system was positioned at ~+155 ppm, closely paralleling the reference shift of the BF_3–methyl-*n*-butyl ether complex, but differing sharply from the value observed for BF_3–acetonitrile. Thus, in compounds containing methoxy and nitrile functional groups, the exclusive interaction site would be the oxygen unshared electron pair. This behavior parallels protonation data which indicate a much greater basicity for methoxy compounds as compared to nitriles.[20]

In several of the remaining systems of Tables I and II, complexing by BF_3 occurred at more than one site in the base. Unfortunately, it cannot be demonstrated conclusively whether these interactions are occurring in different molecules, or at two or more sites in the same molecule. A possible criterion is the temperature dependence of the ligand signal line widths. If complexing is complete at one site, as it is in the ref-

(20) E. M. Arnett, *Progr. Phys. Org. Chem.*, 1, 223 (1963).

erence samples included here, all line widths reflect the same exchange rate, with a possible added factor of quadrupole broadening at nuclei close to the interaction site. When complexing occurs at more than one site, however, the simultaneous occurrence of several exchange paths creates a much more complicated situation. For example, in the BF_3–methoxymethylacetate solution spectra, the $-CH_2OCH_3$ pmr signals definitely show a much greater temperature dependence than the signals of the CH_3CO_2- fragment. Similarly, in the ^{19}F nmr spectra of this system, the signal at +156 ppm, corresponding to bonding at the methoxy group, shows the greater temperature dependence. This situation also prevailed for the other compounds involved in multiple site interactions. Depending on the exchange mechanism, this line width behavior could result from either complexing possibility mentioned above.

A consideration of steric and thermodynamic factors, however, points to complexing with different molecules. Either situation would produce similar entropy changes, so this parameter would not dominate. However, the charge withdrawal which accompanies complexing at one site in a molecule would diminish the basic strengths and complexing tendencies of other sites in the same molecule. Finally, the steric problems posed by BF_3 complexation at two and even three sites (methylacetoacetate, methylpyruvate) in the same molecule argue strongly against this possibility.

The results for methylmethoxyacetate, methoxymethylacetate, and 2-methoxyethylacetate reflect the consequences of differences in functional group basicity, canonical structures, and steric hindrance. For example, in the ^{19}F nmr spectra of the BF_3–methylmethoxyacetate and BF_3–methoxymethylacetate solutions, signals corresponding to binding at the carbonyl (+149 ppm) and methoxy (+156 ppm) linkages are observed. However, while 80% of the BF_3 is bound at the methoxy site in the methylmethoxyacetate system, only 20% is bound at this site in the case of methoxymethylacetate. The ^1H integration data in the latter system agree well with these ^{19}F nmr results. In the absence of steric hindrance, proton basicity studies would predict that complexing at the ether linkage would dominate. However, a previous BF_3 ligand preference study of acetone–ethyl ether mixtures demonstrated that steric hindrance was a factor even in the case of this ether.[13] Similar steric considerations with molecular models of these compounds reveals some hindrance at the methoxy site in both cases, a comparable hindrance at the carbonyl site in methylmethoxyacetate, and severe hindrance at the carbonyl oxygen atom of methoxymethylacetate. Thus, the surprisingly high fraction of BF_3 complexed at this last site must reflect the presence of another process. For both molecules the canonical structures involve only the carboxyl fragment, that is eq 1 for methylmethoxyacetate and eq 2

$$CH_3OCH_2\overset{\overset{O}{\|}}{C}OCH_3 \longleftrightarrow CH_3OCH_2\overset{\overset{O^-}{|}}{C}{=}O^+CH_3 \qquad (1)$$

$$CH_3\overset{\overset{O}{\|}}{C}OCH_2OCH_3 \longleftrightarrow CH_3\overset{\overset{O^-}{|}}{C}{=}O^+CH_2OCH_3 \qquad (2)$$

for methoxymethylacetate. The methoxy site basicity would be essentially unaffected by 1, whereas this site would experience a diminution of its basic strength by the proximity of the partial positive charge in 2. The data of Tables I and II are consistent with this interpretation.

A consideration of the spectra for the BF_3–2-methoxyethylacetate system[17] must include the temperature dependence of the integration data. Thus, complexing dominates at the carbonyl oxygen (60%) at −100°, and at the methoxy site (60%) at −60°. It may be assumed that group basicities and resonance in this molecule would parallel the situation which prevails in its closest structural analog, methoxymethylacetate. This would explain the dominance of the carbonyl site at the lowest temperature. However, molecular models clearly demonstrate that the increased size of 2-methoxyethylacetate results in strong steric hindrance at both the carboxyl and methoxy sites. The lack of temperature dependence for the data of the BF_3–methoxymethylacetate complex implies that basicity and resonance effects are not influenced by this parameter over these small (~40°) temperature ranges. Rather, modifications of the strong steric hindrance must be responsible for the BF_3–2-methoxyethylacetate results. It was not possible to extend the temperature range with this sample because of viscosity and exchange broadening. However, these results are sufficient to emphasize the need for considering all processes which affect complex formation and their possible temperature dependence. It is conceivable, for example, that an organic reaction pathway could be influenced markedly by this behavior.

The results for acetylacetone and methylacetoacetate, particularly the ^{19}F nmr shift and area data of Table II, reflect the ability of these compounds to undergo keto–enol tautomerism. The enol tautomer is the more stable form of pure acetylacetone, ~75%, but the resonance of the ester group of methylacetoacetate occurs at the expense of the enol form and reduces its concentration to a few per cent.[21] In other words, the

$$CH_3\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}OCH_3 \longleftrightarrow CH_3\overset{\overset{O^-}{|}}{C}{=}CH_2\overset{\overset{O}{\|}}{C}OCH_3 \qquad (3)$$

resonance (eq 3) results in a displacement of the tautomeric equilibrium (eq 4) to the ketone form.

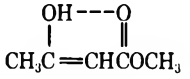
$$CH_3\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}OCH_3 \rightleftharpoons CH_3\overset{\overset{OH}{|}}{C}{=}CH\overset{\overset{O}{\|}}{C}OCH_3 \qquad (4)$$

The data shown in Tables I and II for the BF_3–acetylacetone system were attained after the sample had thoroughly equilibrated. In contrast to the other compounds studied here, the spectral features for this system and to a smaller extent that of the methylacetoacetate sample demonstrated a slow approach to equilibrium. Initially, bound ligand pmr signals were observed in the methyl group region of the BF_3–acetylacetone solution spectrum, and ^{19}F nmr peaks were observed at +136, +148, and +152 ppm, the latter corresponding to BF_3 fractions of 30, 20, and 50%, respectively. After 24 hr at low temperature, the bound ligand signals in the pmr spectrum and the ^{19}F nmr peaks at +148 and +152 ppm were no longer observ-

(21) L. N. Ferguson, "The Modern Structural Theory of Organic Chemistry," Prentice-Hall, Englewood Cliffs, N. J., 1963, Chapter 4.

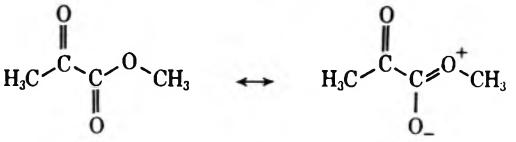
able. These spectra remained unchanged from that point on. The ^{19}F nmr signals at +148 and +136 ppm, respectively, can be attributed to the BF_3–keto complex and the BF_3–enol complex with bonding at the hydroxyl oxygen. This latter conclusion is based on a comparison to the results obtained with 2-hydroxyacetophenone, a structurally similar molecule. The remaining ^{19}F peak observed initially at +152 ppm cannot be assigned quantitatively. At any rate, as the system equilibrates, the most stable complex by far is the BF_3–enol species giving rise to the ^{19}F signal at +136 ppm.

A similar situation prevails in the BF_3–methylacetoacetate solution except, as indicated above, the enol form is not as stable with this molecule. Initially, one ^{19}F nmr peak at +150 ppm was observed for this sample, this position corresponding closely to a BF_3–keto complex. After equilibration, this signal decreases in intensity, and two stronger signals appear at +138 (~58%) and +156 ppm (25%). Thus, complex formation stabilizes the enol form of this compound resulting in the peak at lowest field (+138 ppm). In addition, a BF_3–keto complex is still present at equilibrium and, surprisingly, a complex corresponding to bonding at the ether-type oxygen of the ester group (+156 ppm). This last point is not satisfactorily interpreted but it may be due to the presence of a hydrogen-bonded species of the type



with subsequent complex formation at the ester group.

Finally, a partially successful attempt was made to study the BF_3–methylpyruvate system, because this molecule presents the interesting structural feature of neighboring carbonyl and ester groups. As with several of the compounds listed in Table I, bound ligand signals could not be observed in the pmr spectra. As seen in Table II, however, three ^{19}F nmr peaks were observed, corresponding to complexing at a carbonyl group (+149 and +150 ppm) and an ether-type oxygen (+156 ppm). These results indicate that the primary factor regulating complex formation in this system must be the basic nature of the particular sites. For example, models show no significant steric hindrance to bonding at any site in the molecule. Also, if resonance were the dominant factor, the canonical forms



would repress complex formation at the ester oxygen, a situation which contradicts the observed result. Thus, the overriding factor in this system is the inherently greater basicity of an ether-type linkage as compared to a carbonyl group.

Experimentally these results demonstrate the advantages of slowing ligand exchange to permit the direct study of solution complexes, and the desirability of correlating different types of nmr data, in this case ^1H and ^{19}F measurements. More importantly, the conclusions drawn emphasize the need for considering as many molecular properties as possible, for example, functional group basicity, resonance, tautomerism, and steric hindrance, when trying to determine the mechanism of complex formation. The molecules studied here all exhibit these features to some extent, and an expansion of the program to more complicated ligands is underway.

Acknowledgments.—This work was supported in part by a National Science Foundation Research Grant, GP-9517, and a National Science Foundation Instrument Grant, GP-8347, for the purchase of the Varian HA-100 MHz spectrometer. One of us (A. F.) is the recipient of a National Institutes of Health, Research Career Development Award (5-K4-GM-42334). The authors are indebted to Mr. Richard Perrigan for his assistance in recording the fluorine-19 nmr spectra.

Ring Opening in the Hydroboration of Vinylcyclopropane Systems. A Cyclopropylcarbinyl–Allylcarbinylborane Rearrangement[1]

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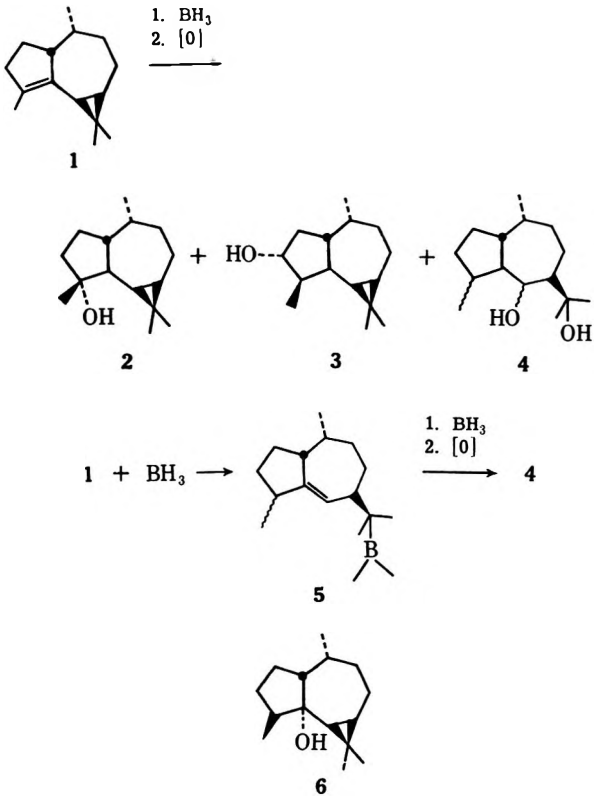
The hydroboration–oxidation of α-cyclopropyl-β,β-dimethylstyrene (**7**) at room temperature gives α-cyclopropylbenzyldimethylcarbinol (**11a**) (12%) and 5-methyl-4-phenyl-1,3-hexanediol (**12a**) (75%). From the hydroboration of **7** at −20° for 1 hr a mixture is obtained which is composed of **7** (72%), cyclopropylisopropylphenylcarbinol (**8a**) (5%), **11a** (4%), *trans*-5-methyl-4-phenyl-3-hexenol (**9a**) (6%), *cis*-5-methyl-4-phenyl-3-hexenol (**10a**) (3%), and **12a** (2%). On the basis of these results the ring opening during the hydroboration of vinylcyclopropanes is rationalized by a stepwise mechanism involving (a) normal hydroboration of the double bond; (b) homoallylic rearrangement of the α-cyclopropylcarbinylborane to an allylcarbinylborane derivative, which may undergo further hydroboration.

The cyclopropane ring does not normally react with diborane in tetrahydrofuran under the usual hydroboration conditions.[2,3] There are, however, a number of reports in the literature describing cyclopropane ring opening in the course of hydroborations of some conjugated vinylcyclopropane systems.[4-6]

Thus the hydroboration–oxidation of α-gurjunene (**1**) was reported to give the isomeric alcohols **2** and **3** in addition to the diol **4** resulting from the opening of the cyclopropane. Alcohol **2** is one of the expected, normal hydroboration products of α-gurjunene. The formation of **3** is the result of isomerization of the initially formed organoborane (precursor of **2**), while the formation of the diol **4** was interpreted in terms of conjugate addition of borane to the vinylcyclopropane system, giving first the homoallylic organoborane **5**, which is then further hydroborated and oxidized. It is worthy of note that Pesnelle and Ourisson did not mention the formation of the angular alcohol **6**, which should also arise from the hydroboration–oxidation of the tetrasubstituted double bond of **1**. The other papers in this field, dealing with the hydroboration of different vinylcyclopropane systems,[5,6] reported the formation of *unsaturated* products in addition to the normal products of hydroboration.



The cyclopropane ring opening during the hydroboration of vinylcyclopropanes may also be rationalized by a multistage mechanism. At the initial stage the hydroboration across the double bond gives rise to the isomeric α- and β-cyclopropylorganoboron compounds, of which the β-cyclopropylorganoborane behaves normally, while the α-cyclopropylcarbinylborane undergoes a homoallylic rearrangement to give the corresponding allylcarbinylborane derivative. Analogous cyclopropylcarbinyl–allylcarbinyl rearrangements have been described involving the cyclopropylcarbinyl anion of magnesium,[7] lithium,[8] and sodium–potassium.[9]

We undertook a study of the hydroboration of a vinylcyclopropane system in an attempt to establish the mechanism of the cyclopropane ring opening during hydroboration.

As a model compound for our studies we have chosen α-cyclopropyl-β,β-dimethylstyrene (**7**) due to the following considerations: (1) it contains a tertiary carbon atom α to cyclopropane; (2) its double bond is tetrasubstituted; (3) it has a phenyl group attached to the carbon atom that bears the cyclopropane. This is desirable since the cyclopropyl group is known to have a directive effect on the hydroboration of an adjacent double bond[10] that tends to increase the placing of the boron atom on the β carbon. The phenyl group is known to have the opposite directive effect;[11] therefore its presence on the carbon atom α to the cyclo-

(1) A preliminary account of this work was presented at the 38th Meeting of the Israel Chemical Society, Beer Sheva, Oct 8–10, 1968; E. Breuer, E. Segall, and S. Sarel, *Israel J. Chem.*, **6**, 14p (1968).

(2) See, for example, H. C. Brown and A. Suzuki, *J. Amer. Chem. Soc.*, **89**, 1933 (1967).

(3) Cyclopropanes do react, however, with diborane in the gas phase at elevated temperature: (a) W. A. G. Graham and F. G. A. Stone, *Chem. Ind. (London)*, 1098 (1957); B. Rickborn and S. E. Wood, *J. Amer. Chem. Soc.*, **93**, 3940 (1971).

(4) P. Pesnelle and G. Ourisson, *J. Org. Chem.*, **30**, 1744 (1965).

(5) W. Cocker, P. V. R. Shanon, and P. A. Staniland, *J. Chem. Soc. C*, 915 (1967).

(6) D. Dopp, *Chem. Ber.*, **102**, 1081 (1969).

(7) D. J. Patel, C. L. Hamilton, and J. D. Roberts, *J. Amer. Chem. Soc.*, **87**, 5144 (1965).

(8) J. A. Landgrebe and J. D. Shoemaker, *ibid.*, **89**, 4465 (1967).

(9) A. Maercker, *Justus Liebigs Ann. Chem.*, **732**, 151 (1970).

(10) S. Nishida, I. Moritani, K. Ito, and K. Sakai, *J. Org. Chem.*, **32**, 939 (1967).

(11) H. C. Brown, "Hydroboration," W. A. Benjamin, New York, N. Y., 1962, pp 113–122.

propane should counterbalance the directive effect of the latter.

Results

The addition of cyclopropyl phenyl ketone to an excess of isopropylmagnesium bromide in ether gave 1-cyclopropyl-1-phenyl-2-methyl-1-propanol (**8a**) in 66% yield.

The dehydration of the latter (**8a**) was first attempted in refluxing acetic anhydride, since this method was proven successful previously with a series of aryl cyclopropyl carbinols.[12] This reaction was found to proceed very slowly with **8a**, and only after prolonged heating it provided a mixture consisting of the desired olefin **7** (30%) and two rearranged acetates, **9b** (53%) and **10b** (18%), which was separated by preparative vapor phase chromatography.

The stereochemistry in the two geometrical isomers (**9b** and **10b**) was deduced from their uv and nmr spectra. The absence of absorption maxima around 240 mμ[13a] in the uv spectra of *both* acetates suggests that the phenyl ring cannot assume coplanarity[13b] with the double bond, probably due to nonbonded interaction between the aromatic ring and the isopropyl group. Consequently, the vinylic proton resonance of the cis isomer **10b** should appear at a higher field than in the trans isomer **9b**. Also the methylene groups of **9b** should resonate at a higher field than those of **10b**, due to a shielding effect of the aromatic ring.[14]

The relevant nmr data of the acetates **9b** and **10b** are listed in Table I.

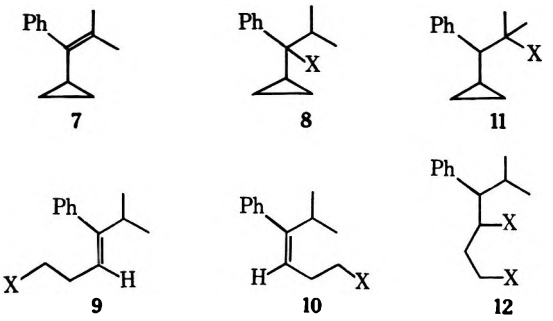
The dehydration of **8a** could be effected more conveniently and in somewhat higher yield (50%) by the use of *p*-toluenesulfonic acid.

Hydroboration–oxidation of **7** was first carried out under the usual reaction conditions. Vpc analysis of the product mixture showed the presence of two products: A (with similar, but not identical retention time with that of alcohol **8a**) and B (of considerably longer retention time) in yields of 12 and 74%, respectively.

TABLE I
NMR DATA OF *cis*- AND *trans*-5-METHYL-4-PHENYL-3-HEXENYL ACETATES

Hydrogens	Chemical shift (*J*, cps) **9b**	**10b**
Aromatic	7.37–7.17 m 3 H 7.13–6.90 m 2 H	7.14 s 5 H
Vinylic	5.43 t (7) 1 H	5.20 t (7) 1 H
$CH_2\alpha$-O	3.92 t (7) 2 H	4.10 t (7) 2 H
CH allylic	2.5 m (6.5) 1 H	3.0 sept (7) 1 H
CH_2 allylic	2.12 q (7) 2 H	2.50 q (7) 2 H
CH_3 acetyl	1.93 s 3 H	2.03 s 3 H
CH_3 isopropyl	1.03 d (6.5) 6 H	1.0 d (7) 6 H

On the basis of elementary analyses and nmr spectra (see Experimental Section) the structure of A was assigned as **11a**, whereas product B is believed to constitute a diastereoisomeric mixture of 5-methyl-4-phenyl-1,3-hexanediols (**12a**). Further support for



a, X = OH
b, X = OAc
c, X = BH_2
d, X = $B(OMe)_2$

the structure of the diol **12a** can be derived from the fact that a product identical in all respects with **12a** was obtained by hydroboration–oxidation of the acetate mixture (**9b** + **10b**), followed by hydrolysis.

Hydroboration of **7** was then carried out at low temperatures. We found that, when **7** is hydroborated at *ca.* −20° (Dry Ice–carbon tetrachloride), and the excess hydride is decomposed at the same temperature (MeOH), followed by oxidation, a complex mixture is obtained.

The products obtained in a typical experiment (1 hr at −20°) are (1) starting material **7** (72%); (2) cyclopropylisopropylphenylcarbinol (**8a**) (5%); (3) α-cyclopropylbenzyldimethylcarbinol (**11a**) (4%); (4) *trans*-5-methyl-4-phenyl-3-hexenol (**9a**) (6%); (5) *cis*-5-methyl-4-phenyl-3-hexenol (**10a**) (3%); (6) 5-methyl-4-phenyl-1,3-hexanediol (**12a**) (~2%).

Compounds **7**, **8**, **11a**, and **12a** were identified by comparison of their retention times with those of the known compounds on several vpc columns. The homoallylic alcohols **9a** and **10a** were identified by comparison with the products of hydrolysis of the homoallylic acetates, **9b** and **10b**.

(12) S. Sarel, E. Breuer, S. Ertag, and R. Salamon, *Israel J. Chem.*, **1**, 451 (1963).

(13) E. A. Braude in "Determination of Organic Structures by Physical Methods," E. A. Braude and F. C. Nachod, Ed., Academic Press, New York, N. Y., 1955: (a) p 153; (b) p 169–170.

(14) Calculations based on a recent paper[15] give values of 5.41 and 5.78 ppm for the chemical shifts of the vinylic protons in **9b** and **10b**, respectively. Comparison of these values with those in Table I indicates that there is very good agreement between the calculated and observed values for the trans acetate **9b**. In contrast, the observed value for the cis acetate **10** differs by 0.58 ppm from the calculated. This difference is presumably a result of the shielding effect of the aromatic ring twisted out of the plane of the double bond.[16]

(15) U. E. Matter, C. Pascual, E. Pretsch, A. Pross, W. Simon, and S. Sternhell, *Tetrahedron*, **25**, 691 (1969).

(16) On the other hand, we noted that the aromatic protons in **10b** appear as a singlet, whereas in **9b** they appear as two groups of complex multiplets in the ratio of 3:2.

The hydrogens of an aromatic ring which is conjugated to double bonds appear usually as a multiplet, whereas loss of conjugation is usually accompanied by the collapse of the multiplet into a singlet.[17,18]

On the basis of the shape of the signals of the aromatic hydrogens in the two acetates alone, one would tend to reverse the structure assignment we forwarded, since of the two structures obviously **9b** is the one in which it would be more difficult for the phenyl group to attain coplanarity with the double bond, and therefore the aromatic hydrogens of **9b** should appear as a singlet. However, since the uv spectra of both acetates indicate lack of conjugation between the phenyl ring and the double bond, we do not consider the arguments concerning the splitting of aromatic hydrogens relevant to our problem. The splitting of the aromatic hydrogens in **9b** is therefore not caused by conjugation of the ring to a double bond.

(17) (a) H. W. Whitlock and Y. N. Chuah, *Inorg. Chem.*, **4**, 424 (1965); (b) N. A. Clinton and C. P. Lillya, *J. Amer. Chem. Soc.*, **92**, 3058 (1970).

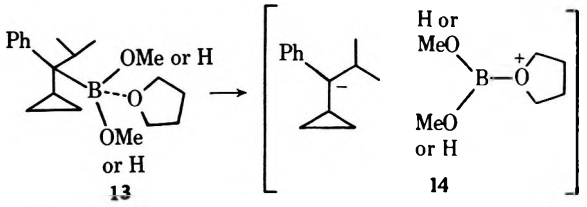
(18) Compare spectra of *cis*- and *trans*-stilbene: "High Resolution NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, spectrum no. 305 and 306.

Discussion

The results presented here indicate that the cyclopropane ring opening that occurs during the hydroboration of α-cyclopropyl-β,β-dimethylstyrene is a stepwise process.

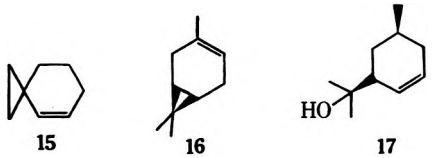
The formation of the cyclopropanic alcohol **8a** in the low-temperature experiment indicates that in the first step the reaction involves only the double bond to yield the organoboranes **8c** and **11c**. The β-cyclopropylcarbinylborane **11c** appears to be stable under these reaction conditions, whereas the α-cyclopropylcarbinylorganoborane **8c** undergoes homoallylic rearrangement to give the unsaturated organoboranes **9c** and **10c**. If this rearrangement occurs in the presence of excess hydride, the rearrangement products **9c** and **10c** undergo further hydroboration to yield a bisboron compound of type **12c**, precursor of the diol **12a**. The actual formation of **12a** was observed both in the room-temperature and in the low-temperature experiments.

The predominance of the unsaturated alcohols **9a** and **10a** over the diol **12a** in the product mixture resulting from the low-temperature reaction indicates that the rearrangement leading to the open-chain organoboranes **9c** and **10c** occurred mainly after the excess hydride was destroyed. It follows, therefore, that not only the cyclopropylcarbinylborane **8c** but also the cyclopropylcarbinlyboronate **8d** is capable of undergoing cyclopropylcarbinyl–allylcarbinyl rearrangement. This suggests that the rearrangement involves a carbanion intermediate, and that the C–B bond-breaking step is being assisted by the methoxyl groups bonded to the boron and/or by the solvent molecules as shown (**13** → **14**).



13 14

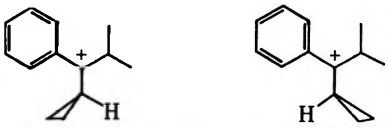
Nishida and coworkers[10] did not observe any cyclopropyl ring opening in the hydroboration of vinylcyclopropane (at −30 to −10°) and of spiro[2.5]oct-4-ene (**15**) (0–20°). The hydroboration of (+)-car-3-ene (**16**) was reported to give some D(−)-*cis*-*m*-menth-4-en-8-ol (**17**), the yield of which was found to depend on the reaction temperature (20–170°).[5]



15 16 17

From the results so far accumulated it is clear that the cyclopropane ring opening occurs with much greater ease with *tert*-cyclopropylcarbinylboranes, in which the C–B bond breaking results in a considerable relief of steric strain, than in the *sec*-cyclopropylcarbinyl boron compounds, in which the rearrangement seems to require elevated temperatures.

Finally it is of interest to point out that the cis/trans ratio of the homoallylic alcohols **9a** and **10a** obtained in hydroboration closely resembles that of the acetates, **9b** and **10b**, resulting from the reaction of **8a** with acetic anhydride. The latter reaction may reasonably be assumed to proceed *via* a carbonium ion mechanism. The ratio of the products **9b**:**10b** indicates that conformation **18** for the carbonium ion is somewhat preferred to conformation **19**, presumably due to non-



18 19

bonded interactions, which are somewhat greater between the cyclopropyl and isopropyl groups, as compared to those between the cyclopropyl and phenyl groups.[19] The isomer distribution of homoallylic alcohols obtained in the hydroboration indicates, therefore, that the conformation of the intermediate in the cyclopropylcarbinyl allylcarbinylborane rearrangement is affected by steric factors similarly to the carbonium ion intermediate.[20]

Experimental Section[21]

Cyclopropylisopropylphenylcarbinol (8a).—Cyclopropyl phenyl ketone (8.4 g, 0.4 mol) in ether (60 ml) was added to a twofold excess of isopropylmagnesium bromide in ether. The reaction mixture was allowed to stand at room temperature overnight and decomposed by 130 ml of saturated ammonium chloride solution. After the usual work-up the carbinol was isolated by distillation: bp 95–100° (2 mm); yield 50.3 g (66%); n^{20}D 1.5290.

The infrared spectrum showed no absorption in the carbonyl region and the OH at 3500 cm^{-1}. The nmr spectrum showed the aromatic hydrogens as a broad multiplet at δ 7.6–7.1 (5 H), the methine CH of the isopropyl group at 2.12 (1 H) (J = 7 cps), two magnetically nonequivalent methyl groups at 0.93 d (3 H) (J = 7 cps) and 0.78 d (3 H) (J = 7 cps), and the cyclopropyl hydrogens at 1.35–0.1 m (5 H).

Anal. Calcd for $C_{13}H_{18}O$: C, 82.10; H, 9.50. Found: C, 81.87; H, 9.22.

Reaction of Cyclopropylisopropylphenylcarbinol with Acetic Anhydride.—A mixture of 9.5 g (0.05 mol) of **8a** and 15.5 g of acetic anhydride was refluxed for 1 week. Gas chromatographic analysis revealed that after this period of time there was no starting material left in the mixture. The reaction mixture was poured into water and ether, and extracted several times with water and then several times with cold 20% sodium hydroxide solution. After drying the ether was removed and the residue was distilled, bp 70–90° (0.8 mm), yield 7.6 g. Gas chromatographic examination of the distillate on several columns revealed that it was a mixture of three compounds in the ratio of 28:54:18 in the order of their increasing retention times. Samples of these components were isolated from the mixture by preparative vpc on a 6 ft × 0.25 in. Apiezon L column at 200°.

Component I was identified as α-cyclopropyl-β,β-dimethylstyrene (**7**). The ultraviolet spectrum in ethanol showed two maxima, 226 nm (ϵ_{mol} 5980) and 241 (4150). The nmr spectrum

(19) The estimated steric effects of the phenyl and the isopropyl groups are −1.44 and −1.71 respectively: T. C. Bruice and W. C. Bradbury, *J. Amer. Chem. Soc.*, **87**, 4838 (1965).

(20) S. Sarel, J. Yovell, and M. Sarel-Imber, *Angew. Chem., Int. Ed. Engl.*, **7**, 577 (1968).

(21) The purification of reagents and solvents and the preparation of borane solution in tetrahydrofuran were carried out as described by Zweifel and Brown.[22] Infrared spectra were measured on a Perkin-Elmer 237 grating spectrophotometer. Ultraviolet spectra were measured in ethanol by a Hillger-Watts Ultrascan spectrophotometer. Nmr spectra were measured by a Varian A-56-60 instrument in $CDCl_3$; all chemical shifts are given in parts per million downfield from TMS. All gas chromatographic work was carried out on a F & M Model 720 dual column programmed temperature gas chromatograph. Microanalyses were carried out by the Hebrew University microanalytical laboratory. All boiling points are uncorrected.

(22) G. Zweifel and H. C. Brown, *Org. React.*, **13**, 1 (1963).

showed the aromatic hydrogens at δ 7.7–6.7 (5 H), methyl hydrogens at 1.82 (3 H) s and 1.42 (3 H) s, and the cyclopropyl hydrogens at 0.7–0.1 (5 H) m.

Anal. Calcd for $C_{13}H_{16}$: C, 90.70; H, 9.30. Found: C, 90.90; H, 9.40.

Component II was identified as the trans acetate **9b**. Its infrared spectrum showed a carbonyl absorption at 1760 cm^{-1}. The ultraviolet spectrum showed one maximum at 224 nm (ϵ_{mol} 5200).

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.40; H, 8.80. Found: C, 77.67; H, 8.69.

Component III was identified as the cis acetate **10b**. Its infrared spectrum showed a carbonyl absorption at 1754 cm^{-1}. The ultraviolet spectrum showed a maximum at 224 nm (ϵ_{mol} 5700).

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.40; H, 8.80. Found: C, 77.57; H, 8.64.

α-Cyclopropyl-β,β-dimethylstyrene (7).—This experiment was best carried out in a vacuum distilling apparatus equipped with a short Vigreux column. *p*-Toluenesulfonic acid (4.3 g, 0.025 mol) was placed in a distilling flask of 25 ml capacity, which was heated in an oil bath to 120°, the whole apparatus being under vacuum of *ca.* 1 mm. Carbinol **8a** (8.6 g, 0.05 mol) was introduced at the fastest possible rate in order to minimize loss of material by resinification. The distillate was collected in a receiver cooled to 0°. During the course of the addition the bath temperature was raised to 180°. At the end of the experiment 4.5 g of distillate was collected in the receiver. Vpc examination revealed that it was the desired olefin in 90% purity, containing approximately 10% starting material and two impurities with retention times very close to that of the main product. Purification could not be effected by distillation; therefore, the crude product was filtered through a silica gel–silver nitrate column in petroleum ether (bp 30–60°), thus giving a gas chromatographically pure product, bp 109° (20 mm), $n^{20}D$ 1.5321. For spectral data and analysis, see previous experiment.

Hydroboration of α-Cyclopropyl-β,β-dimethylstyrene (7) at Room Temperature.—Olefin **7** (2 g, 11.4 mmol) and tetrahydrofuran (5 ml) were placed in a 50-ml hydroboration flask. To this solution 1.67 *M* borane in tetrahydrofuran (13.8 ml, 23 mmol BH_3) was added by means of a syringe. After stirring at room temperature for 24 hr, the excess hydride was decomposed by addition of water (liberation of 1200 ml of hydrogen), and the reaction mixture was oxidized by adding 3 *N* sodium hydroxide (5 ml) and 30% hydrogen peroxide (5 ml) solution. The solution was saturated with sodium hydroxide, the phases were separated, and the aqueous phase was extracted five times with ether. After drying the solution, the ether was removed, and the residue was chromatographed on basic alumina. Alcohol **11a** was eluted by 20% ether in petroleum ether, 0.25 g (~12%). A sample was purified by preparative vpc on a GE SE-30 column at 150°. The nmr spectrum showed δ 7.22 (aromatic, broad s, 5 H), 1.28 (methyl, s, 3 H), and 1.22 (s, 3 H), and a complex multiplet at 2.1–0.1 (7H).

Anal. Calcd for $C_{13}H_{18}O$: C, 82.10; H, 9.50. Found: C, 81.98; H, 9.68.

Diol **12a**, presumably a mixture of diastereoisomers, was eluted from the column by washing with 5% ethanol in ether, 1.75 g (~74%). A sample was purified by preparative glc on a GE SE-30 column at 200°. The nmr spectrum of this product showed the aromatic hydrogens at δ 7.25 (broad s, 5 H), methine α to O at 4.23 (broad, 1 H), methylene α to O at 3.70 (t, J = 7 cps) (2 H), hydroxyl (shifted upon dilution) at 3.18 (broad, 2 H), 2.70–1.94 (complex multiplet, 2 H), 1.65–1.15 (complex multiplet, 2 H), 1.08–0.62 (complex multiplet, 6 H).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 75.00; H, 9.60. Found: C, 74.85; H, 9.62.

Products **11a** and **12a** thus isolated served as external standards for gas chromatographic determination of their yields in subsequent experiments, which, varied in reaction times and the ratios of the reactants, showed no other products.

Thin layer chromatography on silica gel in ether–chloroform (1:1) separated the product mixture to three components. Elution of the components from the plate gave alcohol **11a** and diol **12a**, whereas the least polar, nonvolatile component, which was found to contain boron by qualitative tests, was not investigated further.

Hydroboration of α-Cyclopropyl-β,β-dimethylstyrene (7) at −20°.—To olefin **7** (300 mg) placed in a small hydroboration flask immersed in a Dry Ice–carbon tetrachloride bath, 1.5 *M* borane (2.4 ml) in tetrahydrofuran was added. The solution was kept at −20° for 1 hr, then the excess hydride was decomposed by the injection of methanol (0.5 ml). It was allowed to warm up to room temperature and was oxidized as usual by alkaline hydrogen peroxide. After work-up, gas chromatographic examination (on a 6-ft GE SE-30 column with programming at the rate of 5°/min from 100 to 200°) revealed that the mixture was composed of six peaks. By comparison with the retention times of authentic samples on several gas chromatographic columns the following identifications were made: Peak 1, starting material **7** (72%); peak 2, alcohol **11a** (4%); peak 3, alcohol **8a** (5%); peak 4, trans homoallylic alcohol **9a** (6%); peak 5, cis homoallylic alcohol **10a** (3%); and peak 6, diol **12a** (2%).

Hydroboration of the Mixture of Homoallylic Acetates 9b and 10b.—The mixture of acetates (5 g, 0.021 mol) was hydroborated in tetrahydrofuran with 2 *M* borane in tetrahydrofuran (32.2 ml, 0.064 mol) at room temperature for 24 hr. The excess hydride was decomposed and the reaction mixture was oxidized by the addition of 3 *N* sodium hydroxide solution (10 ml) and 30% hydrogen peroxide (10 ml), and then refluxed for 1 hr. The crude product obtained after work-up showed no carbonyl absorption in the infrared. It was proved to be identical with diol **12a** by comparison of their gas and thin layer chromatographic behavior and of their nmr spectra.

Hydrolysis of the Mixture of Homoallylic Acetates 9b and 10b.—The acetate mixture (1 g) was refluxed with 5 *N* methanolic potassium hydroxide (1 ml) for 3 hr. The product obtained by the usual work-up showed no carbonyl absorption in the infrared. Gas chromatographic examination showed that it contained two products which were found to be identical with peaks 4 and 5 of the low-temperature hydroboration experiment (**9a** and **10a**).

Registry No.—**7**, 34564-76-6; **8a**, 34564-77-7; **9b**, 34564-97-1; **10b**, 34564-98-2; **11a**, 34608-91-8; **12a**, 34599-25-2.

Specific Solvent Effects. VI. The Effect of Solvent Variation on the Sedimentation Behavior of Sodio Diethyl *n*-Butylmalonate

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A sedimentation study has been made of the sodio derivative of diethyl *n*-butylmalonate. In benzene it exists as a polymer of molecular weight 11,400 and appears to be monodispersed. In 1,2-dimethoxyethane (DME) it is monomeric at least up to 0.28 *M* concentrations. The results strongly indicate the formation of micelles with different critical micelle concentrations (CMC) in mixed solvent. There is a linear relationship between the CMC and the DME content in appropriate solvent mixtures. The behavior in DME–cyclohexane mixtures is the same as in DME–benzene. However, dimethylformamide is more effective and tetrahydrofuran is less efficient than DME in raising the CMC in benzene mixtures. These relative activities are explained in terms of specific cation solvation. There is no correlation between the dispersity of the sodium enolate and its rate of alkylation previously measured. Therefore, it is concluded that the solvated monomeric ion pair in equilibrium with the micellar system is, relatively, a kinetically insignificant species.

Previous reports[1] described the marked acceleration by certain additives of the rate of alkylation of the sodium enolate of diethyl *n*-butylmalonate with *n*-butyl halides in benzene solution. It was established that the acceleration arises entirely from an alteration in the ground state of the sodio derivative, and not from an effect on either the alkyl halide or the transition state. Results further suggested that this effect is produced by a specific solvation of the cation acting to dissociate the large ion pair aggregate (mol wt >10,000) of the sodio derivative known to exist in benzene solutions. Later work,[2] however, revealed that no rate maxima were achieved even at the highest attainable concentrations of several effective additives. This meant that, if the suggested dispersal mechanism is the only one operating, some unreactive aggregate must be present under all solvent conditions employed. This appeared, *a priori*, to be rather unlikely because rate maxima were not achieved even in neat solvents as polar as dimethylformamide (DMF) or dimethyl sulfoxide.

The most direct approach to the problem was plainly the examination of the sedimentation behavior of this sodium enolate in benzene alone and in the presence of increasing concentrations of selected additives. Accordingly, for the present work, 1,2-dimethoxyethane (DME) was chosen as the additive for extensive study. In addition, two others were selected for investigation in less detail: DMF because it is more effective and tetrahydrofuran (THF) because it is less effective than DME in accelerating the alkylation reaction.

Experimental Section

Materials.—All reagents used were of the purity specified in the following paper.[3] Stock solutions of the sodio derivatives also were prepared as indicated therein. These solutions were drawn into Hamilton gas-tight syringes of appropriate capacity (1, 2.5, or 5 ml), and solvent dilutions (when necessary) were carried out in the syringes (mixing was effected with a bubble of dry nitrogen).

Sedimentation Studies.—Ultracentrifuge cells (double sector Kel-F coated aluminum centerpieces) were dried for several days in a nitrogen atmosphere over phosphorus pentoxide. Immediately before use the reference side of the cell was filled with solvent and the other side was rinsed twice with the test solution before final filling. All analyses were made on a Spinco Model E analytical ultracentrifuge equipped with photoelectric scanning optics.[4]

It is interesting to note that this system could not have been studied without several recent advances in instrumentation. In these solvent systems the sodio derivative has such a low refractive index increment, dn/dc, that it is impossible to study by light-scattering methods, or by any method requiring Schlieren or interference optics. The need for scanning absorption optics is obvious. The system was also unstable using the standard aluminum-filled Epon centerpieces, but fortunately the Kel-F coated centerpieces became available at the beginning of this study.

Experiments were made using wavelengths ranging from 365 to 290 nm depending on concentration. The equilibrium molecular weights were calculated from the equation

$$M = \frac{2RT}{(1 - \bar{v}\rho)\omega^2} \frac{\mathrm{d} \ln c}{\mathrm{d}r^2}$$

where R = gas constant, T = absolute temperature, $\bar{v}$ = partial specific volume, ρ = density of the solution, c = concentration and is proportional to the deflections of the recorder, r = distance from the center of rotation, and ω = angular velocity. In velocity experiments, sedimentation coefficients were evaluated from a linear least-squares fit of the logarithm of the radial position plotted against time. This radial position was taken as the half-height of the plateau of the tracings. All sedimentation coefficients were normalized to benzene at 20°.

Partial Specific Volume.—The partial specific volume was calculated from densities measured in a precision density meter.[5,6] The value in the various solvent mixtures varied between 0.83 and 0.89 ml/g.

Viscosity Studies.—Viscosity determinations were made in Cannon-Ubbelohde semimicro dilution viscometers, size 50. The flow times were of the order of 200 sec. All determinations were made in a thermostated water bath at 25°

Results

Sedimentation equilibrium experiments in benzene were performed at 26,000 rpm and at concentrations of sodio derivative ranging from 0.072 to 0.015 *M*. The typical plot for equilibrium, *i.e.*, ln *c* *vs.* r^2, in all cases gave a linear response, indicating a monodispersed system. The extrapolated molecular weight at infinite dilution is 11,400 (Figure 1).

The results of sedimentation velocity experiments in the same solvent are shown in Figure 2. At very low concentrations there is a marked increase in the sedimentation coefficient with an S^0 equal to 1.6*S*. These

(1) H. E. Zaugg, B. W. Horrom, and S. Borgwardt, *J. Amer. Chem. Soc.*, **82**, 2895, 2903 (1960): parts I and II in the series, "Specific Solvent Effects."

(2) H. E. Zaugg, *ibid.*, **83**, 837 (1961), part IV.

(3) H. E. Zaugg, J. F. Ratajczyk, J. E. Leonard, and A. D. Schaefer, *J. Org. Chem.*, **37**, 2249 (1972).

(4) H. K. Schachman, L. Gropper, S. Hanlon, and F. Putney, *Arch. Biochem. Biophys.*, **99**, 175 (1962); K. Lamers, F. Putney, J. Z. Skinberg, and H. K. Schachman, *ibid.*, **103**, 379 (1963).

(5) Model OM2C purchased from A. Parr, Graz, Austria.

(6) H. Stabinger, H. Leopold, and O. Kratky, *Monatsh. Chem.*, **98**, 436 (1967).

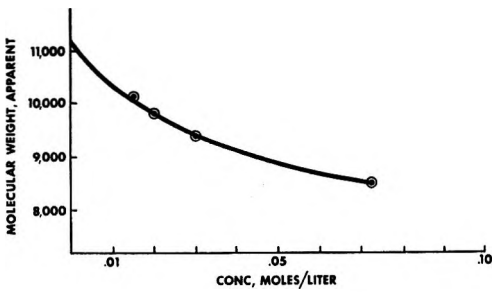

Figure 1.—Concentration dependence of sedimentation equilibrium molecular weight. The value at infinite dilution is 11,400.

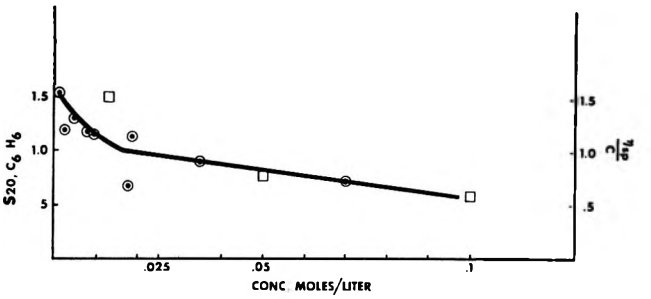

Figure 2.—Concentration dependence of the sedimentation coefficient and intrinsic viscosity. ⊙ = sedimentation, □ = intrinsic viscosity.

results are consistent with those obtained in the sedimentation analyses of polyelectrolytes. That this phenomenon is due to a charge effect is verified by an increase in S_{20}, C_6H_6 from $0.7S$ to $1.5S$ at 0.048 M and an increase in apparent molecular weight from 9400 to 11,400 in the presence of sodium hexylene glycol monoborate[7] (NaHGM), serving as a soluble small electrolyte to quench charge effects.

Calculations of the frictional ratio, f/f_0,[8] with and without salt gave values of 1.11 and 1.24, respectively, which are values consistent with a spherical shape.

Intrinsic viscosity determinations (Figure 2) gave results consistent with the sedimentation data, showing a marked concentration dependence of the results.

When the solvent is changed from benzene to DME a completely different sedimentation picture is obtained. Attempted equilibrium analyses with concentrations from 0.04 to 0.28 M failed to show a concentration distribution, indicating the absence of polymeric material. Sedimentation velocity studies at 68,000 rpm failed to show a sedimenting boundary confirming the results of the equilibrium method. In fact, long time velocity experiments eventually showed typical equilibrium-like distributions and calculations of molecular weight gave values of 320 at 0.28 M, 274 at 0.14 M, 318 at 0.08 M, and 270 at 0.07 M. All of these values are consistent with that of the monomer (mol wt, 238).

Various mixtures of benzene and DME were employed to determine whether a correlation could be found between the per cent DME added and the amount of polymer present. Initial determinations at concentration of DME greater than 50% and a sodio concentration of 0.06 M showed no boundary formation, indicating absence of polymer. When these patterns were calculated as equilibrium results they gave values for molecular weight consistent with monomer. On the other hand, at lower concentrations of DME and the same concentration of sodio derivative a change occurred in the amount of sedimentable material. The lower the concentration of DME the less the amount of monomer. This can be seen experimentally as an increase in nonsedimentable material at the meniscus as the per cent DME increases. A typical result is shown in Figure 3. A log–log plot of the concentration at the meniscus *vs.* DME concentration gives a straight line with a slope approximating unity (Figure 4).

Studies also were made with three other solvent systems at 0.05 to 0.06 M concentrations of sodio derivative: THF and DMF in benzene and DME in cyclohexane. In every instance the salt was rendered completely monomeric well before the medium consisted entirely of the additive. The approximate concentrations of additive where this occurred in benzene were DMF, 3–5%; DME, 50%; and THF, 70%. The variation in meniscus concentration of the totally monomeric state among the four systems reflects the experimental inability exactly to reproduce salt concentrations in the four runs. It is interesting, however, that extrapolation of the DME–cyclohexane line to the much higher apparent concentration of the DME–benzene experiment gives nearly the same solvent composition (50:50) for the break point.

A series of velocity runs also were made at a constant DME concentration (15%) and variable sodio concentration. The results, plotted as the per cent sedimentable material, are shown in Figure 5. As can be seen, a distinct break in the curve occurs at a sodio concentration of 0.013 M. Above this value the amount of polymer increases rapidly. Attempts at equilibrium runs at this concentration of DME were not reproducible and studies of concentration at three cell positions *vs.* time showed that there is no time at which an equilibrium exists. There is no obvious explanation for this phenomenon.

To ensure that there was no pressure effect from the ultracentrifuge, an experiment was conducted in which the meniscus concentration was studied as a function of speed at constant $\omega^2 t$. At all speeds the meniscus concentration was identical, indicating no significant pressure effect.

Discussion

The results in benzene showing a monodispersed molecular system are surprising. It indicates that this system is not of a typical synthetic polymer type, generally characterized by a high degree of polydispersity. Confirmation of the monodispersity was obtained when molecular weight distribution calculations by the method of Scholte[9] also showed only one molecular species present. While our calculations by this method can be questioned (it requires the use of a θ solvent and benzene is obviously not a θ solvent, as seen in Figure 2), the finding of only one molecular species seems unequivocal. Indeed, in a monodispersed system in a non-θ solvent, the only discrepancy appears to be a value for molecular weight which is lower than that measured under conditions for which corrections can be made for nonideality.

(7) Purchased from U. S. Borax Research Corp.

(8) T. Svedberg and K. O. Pedersen, "The Ultracentrifuge," Johnson Reprint Corp., New York, N. Y., 1959, p 40.

(9) T. G. Scholte, *J. Polym. Sci., Part A-2*, **6**, 111 (1968).

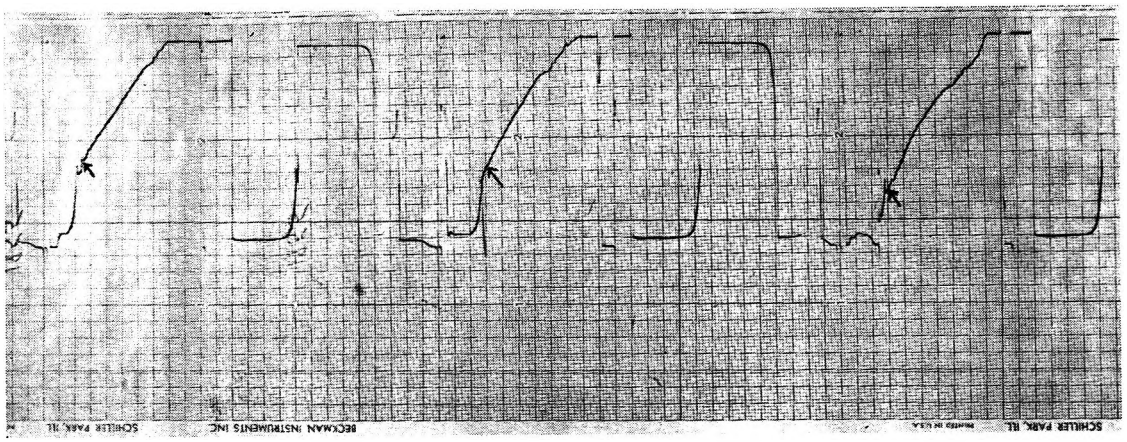

Figure 3.—Photoelectric scans of sodio derivative with varying amounts of DME added. From left to right, 20% DME, 15% DME, and 5% DME in benzene. Scans are at 315 nm, scan time of 30 sec with a photomultiplier slit of 0.14. Scans are at 128 min after reaching speed of 68,000 rpm (336,000*g*).

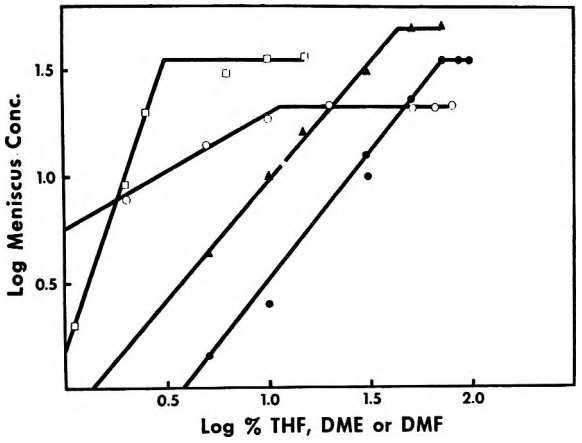

Figure 4.—Log–log plot of meniscus concentration in arbitrary units from the ultracentrifuge scan *vs.* per cent additive: ●, THF in benzene; ▲, DME in benzene; ○, DME in cyclohexane; □, DMF in benzene. (Meniscus concentration is proportional to monomer content.)

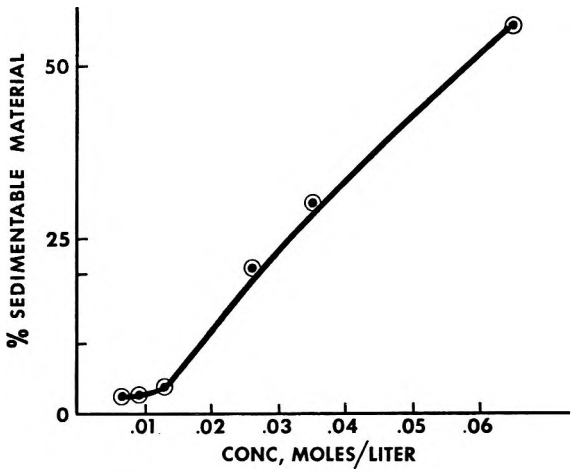

Figure 5.—Determination of per cent sedimentable component *vs.* sodio concentration at 15% DME. Per cent sedimentable component = (plateau concentration − meniscus concentration)/plateau concentration.

The most favorable interpretation of our results then would appear to be that of micelle formation. This is consistent with the fact that the system is monodispersed and also with the size of the polymer, about 40–50 monomeric units. The observation of micelles of this type in nonpolar organic solvents is not new. Ekwall[10] and Peri[11] have both observed the occurrence of such structures and have pointed out the inverse nature of these micelles, in which the hydrophobic moiety is on the outside and the charge is located in the inside of the structure.

We would suggest then that the critical micelle concentration (CMC) in benzene is at very low concentrations and that the amount of free monomer is very small. We were unable to test this hypothesis since spectral interference by benzene restricted the minimum concentration at which determinations could be made. In cyclohexane, however, two runs at 0.01 and 0.005 *M* salt concentration both gave values for a CMC of 0.003 *M*. In DME we would then postulate that either no micelle can exist or that the CMC for this solvent is higher than 0.28 *M*, which is the highest concentration studied. These two postulates would lead naturally to the concept that in mixtures of DME and benzene there would be a relationship between DME content and CMC.

This interpretation of our findings is confirmed in two ways. At 0.06 *M* sodio derivative concentration and varying DME concentrations one gets a linear correlation with meniscus concentration (CMC) until at approximately 50% DME a break occurs. This means that at 50% DME the critical micelle concentration is approximately 0.06 *M*. Also, at a constant DME concentration of 15% and varying the concentration of sodio derivative, the amount of sedimentable material increases sharply past 0.013 *M*. Again, this indicates a CMC of 0.013 *M* at 15% DME. Thus, it has been possible to demonstrate a CMC by varying the concentration of either solvent or solute.

The data of Figure 4 clearly suggest that the mechanism of formation of the monomeric ion pair involves specific solvation by the additive and is not a bulk solvent effect. In the first place, THF and DME are quite different in action even though their bulk properties have been found to be remarkably similar.[12] Secondly, the order of effectiveness of the three additives, DMF > DME > THF, is the same as that for their efficiency in specifically solvating alkali cations, suggesting that in-

(10) P. Ekwall, *J. Colloid Interfac. Sci.*, **29**, 16 (1969).
(11) J. B. Peri, *ibid.*, **29**, 6 (1969).
(12) C. Carvajal, K. J. Tölle, J. Smid, and M. Szwarc, *J. Amer. Chem. Soc.*, **87**, 5548 (1965).

creasing the effective size of the cation by specific solvation inhibits the tendency to form micelles. In a spherical *inverse* micelle of this type, it is obvious that the cations must be small relative to the anions to permit them to be encapsulated in a lipophilic anionic shell. It is interesting that, of many benzene-soluble electrolytes studied by Kraus,[13] only those with a large lipophilic ion and a relatively small counterion showed a particular tendency to agglomerate to form aggregates of high association number.

Finally, the results of the present work provide a clear answer to the problem posed in the introductory paragraph. There is no quantitative correlation between the alkylation rate and the disperisty of the sodium enolate. Sedimentation studies were conducted at salt concentrations equal to or higher than the rate measurements.[1,2] Yet at additive concentrations providing 100% monomer at these salt concentrations no rate maxima are observed.[14] Indeed, no significant discontinuities in log–log plots of rate *vs.* solvent composition are observable for the three additives studied in the present work. From these observations it can be concluded that the solvated monomeric ion pair that is in equilibrium with the micellar system is a kinetically insignificant species compared to some others that must be present in these solvent systems.

Registry No.—Sodio diethyl *n*-butylmalonate, 22600-93-7.

(13) C. A. Kraus, *J. Chem. Educ.*, **35**, 330 (1958); *J. Phys. Chem.*, **60**, 129 (1956).

(14) See Figure 1 of ref 2, or Figure 1 of ref 3.

Specific Solvent Effects. VII. Ion-Pair Processes in the Alkylation of Alkali Enolates

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The observed lack of a common-ion rate depression for the alkylation of sodio diethyl *n*-butylmalonate in DMF shows that at the substrate concentrations used ($\sim 10^{-1}$ *M*) this reaction is an ion-pair process. Proton magnetic resonance studies have been added to previous uv studies to confirm the strong tendency of malonate ions to form tight ion pairs with alkali cations, even in DMF. The kinetic and sedimentation properties of this system in binary solvent mixtures can be reconciled by postulating that, in THF, DME, and DMF (and their mixtures with benzene or cyclohexane), the reactive species is an ion pair more highly solvated than the one shown to be in equilibrium with the micellar system (*cf.* preceding paper). However, the kinetic behavior in the presence of the powerful alkali cation solvator, dicyclohexyl-18-crown-6 polyether, indicates that, in this case, the monosolvated ion pair is the reactive species.

In the preceding study[1] it was found that, in certain mixtures of benzene with three aprotic solvents (S = THF, DME, or DMF), sodio diethyl *n*-butylmalonate (A^-Na^+) consists of at least three species in equilibrium.

$$\underset{\substack{n \sim 50 \\ 1}}{(A^-Na^+)_n} \rightleftharpoons \underset{2}{nA^-Na^+} \overset{nS}{\rightleftharpoons} \underset{3}{nA^-Na^+ \cdot S}$$

In benzene the micelle **1** is the predominant form. In the pure solvent, S, the solvated ion pair **3** and presumably other monomeric forms derived from it are the only detectable species. Results also indicated that specific *cation* solvation by the additive accounts for the equilibrium shift from **1** to **3**. Because of the absence of a quantitative correlation between the increase in concentration of **3** and the previously measured[2] acceleration in the rate of alkylation of A^-Na^+ under identical conditions of solvent variation, the relative kinetic insignificance of **3** was a necessary conclusion. Therefore, other species derivable from **3** must be the reactive forms accounting for the observed rate acceleration. Only two general possibilities remain: more effectively solvated (and more reactive) ion pairs,[3] and "free" anions (A^-).

Previous work[6] demonstrated the lack of a correlation between dielectric constant (and dipole moment) of the additive and its effect on the alkylation rate. Although this would tend to exclude the "free" anion, A^-, as a kinetically important species, a more direct experimental test of this conclusion is included in the present work: a probe of the effect of added salts (both Na^+ and Li^+) on the rate of alkylation of A^-Na^+ in DMF. Because these experiments were conducted at fairly high salt concentrations, their validity was tested using identical conditions in the alkylation of sodio-3-phenyl-2-benzofuranone. Ultraviolet spectral studies[7] have shown that the capacity of this enolate to form ion pairs in dilute DMF solutions is distinctly inferior to that of enolates structurally similar to malonate.

To show that this difference in ion pairing ability extends to the more concentrated solutions used in the rate studies, the effect of dilution on the nmr spectra of the lithium and sodium salts of both diethyl malonate and 3-phenyl-2-benzofuranone were compared in the present work. Also, to support the validity of this method, alkali salts of two phenolate ions, differing widely in ion pairing capacity, were compared.

Finally, to examine further the question of more effectively solvated ion pairs as the kinetically important species in the sodiomalonate alkylation, four more

(1) Part VI: G. H. Barlow and H. E. Zaugg, *J. Org. Chem.*, **37**, 2246 (1972).

(2) H. E. Zaugg, *J. Amer. Chem. Soc.*, **83**, 837 (1961).

(3) The concept of multiple ion pairs has become firmly grounded in the chemical literature relating to the behavior both of carbonium ions[4] and of carbanions.[5]

(4) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, pp 167–171.

(5) T. E. Hogen-Esch and J. Smid, *J. Amer. Chem. Soc.*, **88**, 307, 318 (1966); M. Szwarc, *Science*, **170** (3953), 23 (1970).

(6) H. E. Zaugg, *J. Amer. Chem. Soc.*, **82**, 2903 (1960).

(7) H. E. Zaugg and A. D. Schaefer, *ibid.*, **87**, 1857 (1965).

binary solvent systems were studied using the rate of the standard alkylation as a probe. Of special interest was the behavior of the powerful sodium ion solvator, dicyclohexyl-18-crown-6 ether.[8]

Experimental Section

Materials.—Benzene,[2] *n*-butyl bromide,[2] cyclohexane,[7] diethyl *n*-butylamalonate,[2] and dimethylformamide[7] were of the purity previously specified. Reagent grade 1,2-dimethoxyethane (DME) was stored in a column (3 × 45 cm) of basic alumina (activity grade I) and drawn off just before use. Sodium hydride was in the form of a 50–60% dispersion in mineral oil, and lithium hydride was in the powdered, nondispersed form. 3-Phenyl-2-benzofuranone[9] was recrystallized to a constant melting point (114–116°) from 2-butanone. Dicyclohexyl-18-crown-6 ether was prepared and purified by the method of Pedersen[8] and was used as a mixture of geometric isomers. The following commercially available compounds were purified by distillation or recrystallization: *p*-cresol, bp 56° (1 mm); *p*-nitrophenol, mp 114–114.5° (sublimed); and diethyl malonate, n^{25}D 1.4134, 99.7% (vpc). Sodium *p*-nitrophenoxide was prepared by a method reported previously.[7]

Lithio Diethyl Malonate.—To a stirred, cooled solution of lithium ethoxide (from 0.72 g, 0.09 mol of LiH) in 100 ml of absolute ethanol, diethyl malonate (16 g, 0.1 mol) was added dropwise. After warming to room temperature, the solution was filtered from a small amount of insoluble material and concentrated to dryness under reduced pressure (water pump). The residual, white solid was slurried in dry ether, collected at the filter, and washed with dry ether. Drying at 80° under reduced pressure gave the pure salt.

Anal. Calcd for $C_7H_{11}LiO_4$: C, 50.61; H, 6.68. Found: C, 50.37; H, 6.72.

Kinetics.—All tabulated second-order rate constants were determined under pseudo-first-order conditions using a refinement of the method previously described.[2,10] Stock solutions of the sodio derivative in the appropriate solvent (cyclohexane, benzene, DME, or DMF) were prepared by magnetically stirring, in a nitrogen atmosphere, the acid (diethyl *n*-butylmalonate or 3-phenyl-2-benzofuranone) with an excess of sodium hydride in a cylindrical reaction vessel (45–50-ml capacity) made to fit the cups (3 cm diameter × 10 cm deep) of a standard centrifuge. The supernatant solution was decanted from the centrifuged excess hydride, in an atmosphere of nitrogen, through glass wool into a 50-ml conical storage vessel using the apparatus and procedure previously described for the handling and storage of a Grignard reagent[11] (note especially Figure 4 of ref 11). Stock solution was transferred from the conical storage vessel to the reaction vessel using a Hamilton gas-tight syringe fitted with a 23-gauge needle. The reaction vessel was a simple flat-bottomed cylinder (*ca.* 15-ml capacity) with a single opening (5–6-mm i.d.) at the top suitable for closure with a rubber septum (sleeve stopple). The only critical dimension was a less than 2-in. distance from the top of the septum to the bottom of the vessel. All reactions were carried out so that the combined volumes of reactants and diluents totaled 10 ml. At appropriate time intervals, 1-ml aliquots were removed using a Hamilton gas-tight syringe equipped with a 2-in. 23-gauge needle. These aliquots were quenched in an excess of standard hydrochloric acid and back-titrated with standard sodium hydroxide solution. The concentration of the original stock solution was similarly measured using three 2-ml aliquots. Nearly all reactions were carried well past 50% of completion and many of the faster ones to the 75–90% range. The data for each run were subjected to statistical analysis for determination of the slope and standard deviation from linearity of the plot of log c *vs.* time, where c = concentration of sodio derivative.

To test the reproducibility of results by the new procedure, the rates of alkylation (*n*-C_4H_9Br) at 25° of sodio-*n*-butylmalonic ester at two concentrations of dimethoxyethane (DME) in benzene were determined and compared with corresponding rates determined by the old procedure. In 1.44 *M* DME three separate runs gave 10^5k_2 (M^{-1} sec^{-1}) = 4.51, 4.59, and 5.02, compared to 4.73–4.74 by the old procedure (see Figure 1 of ref 2). In 1.92 *M* DME three runs gave 10^5k_2 = 6.81, 7.07, and 7.18 compared to 6.34 by the old method.

Also, to check the bimolecularity of the rate law, four determinations (at 25°) were carried out under second-order conditions (equimolar concentrations of the two reactants) in 1.905 to 1.928 *M* concentrations of DME. Although reproducibility was poorer, the range of k_2's (5.33–6.68 × 10^{-5}) so measured encompassed the range (6.31–6.39 × 10^{-5}) obtained under pseudo-first-order conditions (ref 2, Figure 1).

Nmr Measurements.—Proton magnetic resonance spectra were obtained using a Varian Model A-60 spectrometer. The temperature of all measurements was 33 ± 2°. Tetramethylsilane in solution was the reference standard.

DMF solutions of the salts were prepared by treating solutions of the organic acids of appropriate concentration with excess amounts of sodium or lithium hydride using a glove-box procedure previously described.[7] After completion of the reaction, the clear (filtered or supernatant) solution was transferred by pipette to an nmr tube, stoppered with an air-tight closure, and transferred immediately from the glove-box to the spectrometer. As independent checks on the method, it was found that solutions prepared by dissolving pure solid sodium *p*-nitrophenoxide and solid lithio diethyl malonate in DMF gave spectra identical with those obtained using comparable solutions prepared by the foregoing procedure.

Results

Kinetics.—The effects of added salts on the alkylation rates in DMF of the two sodio derivatives are given in Table I. These data reveal the absence of a

TABLE I

SALT EFFECTS ON THE RATES OF ALKYLATION AT 25° IN DMF OF DIETHYL SODIO-*n*-BUTYLMALONATE (A) AND OF SODIO-3-PHENYL-2-BENZOFURANONE (B) WITH *n*-BUTYL BROMIDE

A			B		
Salt	Concn, *M*	10^5k_2, M^{-1} sec^{-1}	Salt	Concn, *M*	10^5k_2, M^{-1} sec^{-1}
None	0	323 ± 6	None	0	33.4 ± 0.4
		345 ± 7			34.6 ± 1.1
		339 ± 5[a]	$NaClO_4$	0.103	24.9 ± 0.3
$NaClO_4$	0.101	338 ± 3			25.4 ± 0.4
		332 ± 3			25.7 ± 0.2
$LiClO_4$	0.100	35.0 ± 0.8			
	0.101	46.2 ± 0.5	$LiClO_4$	0.103	19.6 ± 0.3
					21.2 ± 1.2

[a] From ref 2.

significant common-ion effect on the alkylation of the sodio malonate (A) in this solvent. A marked cation effect, however, is evidenced by the 7–8-fold decrease in rate observed in the presence of 0.1 *M* lithium perchlorate.

In contrast, a significant common-ion rate depression is observable for sodio-3-phenyl-2-benzofuranone (B) in DMF. A cation effect is detectable as well for B, but not to the extent observed for A.[12] It should be noted that B, like A, alkylates exclusively at carbon. Hence, no ambident alkylations are involved here.

Four binary solvent effects on the rates of alkylation of sodio *n*-butylmalonate were studied in the present work. They are summarized in Table II and plotted

(8) C. J. Pedersen, *J. Amer. Chem. Soc.*, **89**, 2495, 7017 (1967); **92**, 386 (1970).

(9) A. Bistrzycki and J. Flatau, *Ber.*, **28**, 989 (1895).

(10) H. E. Zaugg, B. W. Horrom, and S. Borgwardt, *J. Amer. Chem. Soc.*, **82**, 2895 (1960).

(11) H. E. Zaugg and W. M. Lauer, *Anal. Chem.*, **20**, 1022 (1948).

(12) Similar salt effects were studied in DME solution. Marked cation (Li^+) effects were observed for both A and B, but no significant common-ion rate depression was detectable for either salt. Although DME clearly does not prevent cation exchange, its relatively low dielectric constant presents the possibility that, unlike the situation in DMF (*cf.* Table IB), the absence of a common-ion rate depression for B is caused by insufficient dissociation of $NaClO_4$.

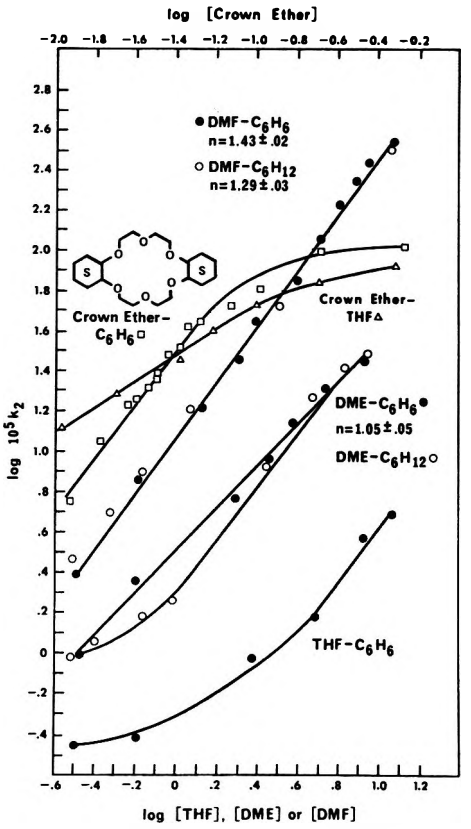

Figure 1.—Log–log plots of rates of alkylation at 25° of diethyl sodio-*n*-butylmalonate with *n*-butyl bromide in seven solvent systems. (Except for the crown ether solutions, the right ends of the lines represent molarities of neat additives diluted only by the reactants.)

TABLE II

RATES OF ALKYLATION AT 25° OF DIETHYL SODIO-*n*-BUTYLMALONATE WITH *n*-BUTYL BROMIDE IN FOUR BINARY SOLVENT SYSTEMS

Concn, *M*	$10^5 k_2$, M^{-1} sec^{-1}	Concn, *M*	$10^5 k_2$, M^{-1} sec^{-1}
A. Dicyclohexyl-18-crown-6 Ether in Benzene		B. DME in Cyclohexane	
0.0116	5.72 ± 0.17	0.301	0.93 ± 0.02
0.0164	11.2 ± 0.8	0.388	1.15 ± 0.01
0.0228	17.0 ± 0.8	0.684	1.48 ± 0.02
0.0249	18.3 ± 1.3	0.954	1.84 ± 0.02
0.0290	21.1 ± 1.1	2.820	9.11 ± 0.22
0.0305	23.0 ± 1.2	4.720	18.7 ± 0.6
0.0313	23.3 ± 2.0	6.710	25.5 ± 0.1
0.0358	30.6 ± 1.2	C. DMF in Cyclohexane	
0.0406	32.7 ± 0.8	0.308	2.91 ± 0.06
0.0447	42.1 ± 1.7	0.464	4.97 ± 0.09
0.0509	43.2 ± 0.5	0.681	7.69 ± 0.13
0.0741	51.3 ± 1.2	1.194	15.96 ± 0.55
0.1015	63.6 ± 0.5	3.293	53.1 ± 0.6
0.202	95.4 ± 1.6	D. Dicyclohexyl-18-crown-6 Ether in THF	
0.527	138.1 ± 2.4	0.01	13.5 ± 0.5
		0.02	19.7 ± 0.4
		0.03	24.5 ± 0.3
		0.04	29.7 ± 0.5
		0.06	41.1 ± 0.6
		0.10	55.3 ± 0.5
		0.20	69.2 ± 0.9
		0.50	84.7 ± 1.2

in Figure 1 along with three others from previous work.[2] Of interest is the observation that the kinetic order of

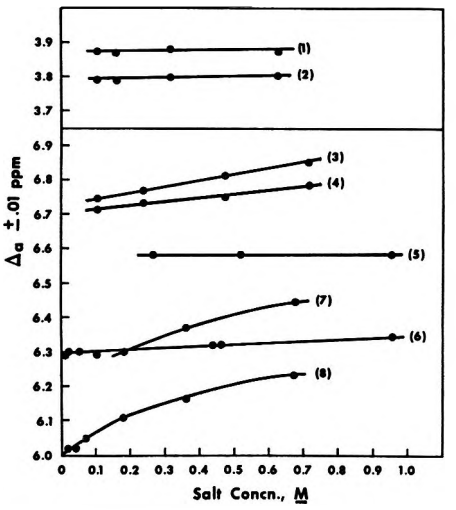

Figure 2.—Effect of concentration on the chemical shifts (Δa) in DMF of protons in the anions of alkali salts: α-H of lithio (1) and sodio (2) diethyl malonate; most intensea romatic resonance peak of lithio- (3) and sodio- (4) 3-phenyl-2-benzofuranone (not a true chemical shift); ortho H of lithium (5) and sodium (6) *p*-cresolate; ortho H of lithium (7) and sodium (8) *p*-nitrophenolate.

participation (n)[13] of DMF is roughly the same in both benzene and cyclohexane mixtures, and is virtually constant (*i.e.*, gives a linear log–log plot) over the whole range of solvent compositions studied. Although DME exhibits a constant unit participation order over the whole range of mixtures with benzene, in cyclohexane there is a slight deviation from this line.

Especially noteworthy is the high activity exhibited by the crown ether. In benzene solutions only 0.036 *M* in crown ether the alkylation rate is already equal to that observed in neat (8.70 *M*) DME. Significantly, however, this high activity does not increase indefinitely. Although the participation order of the crown ether at low concentrations (0.01–0.05 *M*) is constant and roughly equal to that of DMF (1.3–1.4), it begins to decline at 0.05 *M* and approaches zero at 0.5 *M* concentration (*i.e.*, no further rate increase with increased concentration of additive). A similar approach to a slightly lower rate maximum is also characteristic of the crown ether in THF.[14] Initial participation orders in this system are necessarily lower than in crown ether–benzene because the base rate in the latter (*i.e.*, in neat benzene) is much lower than in the former (*i.e.*, in neat THF).[15]

Nmr Measurements.—Figure 2 shows the effect of concentration change on the chemical shifts of selected protons in four pairs of alkali salts (Li^+ and Na^+) including two enolates (1–4) and two phenolates (5–8). In the range of concentrations studied (0.01–1.0 *M*), the presence of ion pairs in all four systems

(13) Given by the slope of the log–log plots in Figure 1.

(14) Because rate measurements at higher concentrations of crown ether in benzene were much less reproducible than in THF, the difference between the two rate maxima may not be significant. The maximum observed in THF is the more reliable one.

(15) It is noteworthy that two diazapolyoxamacrobicyclic compounds[16] (one diamine and one diamide), kindly supplied by Professor J. M. Lehn, produced marked accelerations in the alkylation nearly equal to the effect of crown ether. The powerful alkali cation solvating properties of these polydentate ligands also has been amply demonstrated.[17]

(16) J. M. Lehn, J. P. Sauvage, and B. Dietrich, *Tetrahedron Lett.*, 2885, 2889 (1969); *J. Amer. Chem. Soc.*, **92**, 2916 (1970).

(17) J. M. Lehn, *Angew. Chem., Int. Ed. Engl.*, **9**, 175 (1970); B. Metz, D. Moras, and R. Weiss, *Chem. Commun.*, 217 (1970).

is clearly shown by the uniformly greater deshielding effect of Li^+ on the selected protons.

The influence of concentration change, however, is quite different for the two pairs of enolate salts. A barely significant effect is evident for the two malonate salts (1, 2),[18] but for the benzofuranone salts (3, 4) dilution results in a diminution of the cationic deshielding effect, which is more marked for the lithium than for the sodium salt. This convergent tendency of lines 3 and 4 suggests that, at sufficiently low concentrations, the cation effect should disappear. Previous uv-spectral examination of DMF solutions of 3 and 4 has shown that at concentrations of the order of 10^{-4} *M* the cation effect has indeed vanished.[7]

The insensitivity of the electronic transition energy of malonate anions to changes in environmental charge prevented experimental examination of ion pairing in this system at low concentrations.[7] However, in the closely related β-diketone system (*e.g.*, 2-4-pentanedione) the presence of ion pairs could be seen[7] even at 10^{-4} *M* concentrations in DMF.[19]

Similar contrasting behavior is revealed in the two phenolate systems (5–8). Both salts of *p*-cresol (5, 6) exhibit the insensitivity to dilution characteristic of tight ion pairs, while salts of the stronger acid, *p*-nitrophenol (7, 8), show a greater tendency to dissociate.[20]

Consistent with these observations are the previous findings[7] that at $\sim 10^{-4}$ *M* concentrations in DMF, ion pairs of 5 and 6 are still clearly visible (uv), but are no longer detectable for 7 and 8.

Discussion

The absence of a common-ion rate depression for the alkylation of sodio diethyl *n*-butylmalonate in DMF shows that this reaction is essentially an ion-pair process. The strong tendency of malonate ions to form tight ion pairs even in DMF, as indicated by the nmr experiments, is thus corroborated by this kinetic behavior. This is not to imply that whatever "free" anions are present in DMF[19] are unreactive. At the concentrations of sodiomalonate used in the present study (purposely rather high to approximate preparative conditions), the concentration of "free" anions is clearly so low compared to that of reactive ion pairs that the latter furnish the only *detectable* kinetic pathway. Furthermore, because all other solvent systems used in this work represent media of lower dielectric constant than DMF, it is safe to conclude that all of the sodiomalonate alkylations studied represent nearly pure ion-pair processes.

What, then, is the nature of the reactive ion pairs? The sedimentation studies[1] have already ruled out the initially solvated ion pair **3**, at least for the three additives THF, DME, and DMF. However, the kinetic observations for these additives (Table II and Figure 1) are explainable simply in terms of more highly solvated ion pairs **4** as the reactive species.[21] It is reasonable to expect that the more donor sites that are accommodated by the cation, the more its charge will tend to become neutralized with a consequent increase in the nucleophilicity of the associated anion.

$$\underset{\mathbf{3}}{A^-Na^+\cdot S} \overset{S}{\rightleftharpoons} \underset{\mathbf{4}}{A^-Na^+\cdot S_2}$$

Thus, the formation of **4**, like **3**, involves specific solvation of the cation. In accord with this view is the observation that the rate accelerations produced by either DMF or DME are only slightly affected by a change from benzene to cyclohexane. Also, the order of effectiveness of the three additives, DMF > DME > THF, is the same as that for their efficiency in specifically solvating alkali cations. Indeed, relative to the other two, the monodentate ether, THF, is such a poor specific cation solvator that high concentrations are required to produce appreciable amounts of **4**, thus accounting for the upward curvature of its log–log plot (Figure 1). However, even the best of the three additives (DMF) is still not active enough to shift the equilibrium, **3** ⇄ **4**, completely to the right, since no rate maximum is observed even in neat additive.

The polydentate donor, crown ether, however, presents a different picture. Its powerful cation solvating ability is clearly reflected in its extraordinary capacity to accelerate the alkylation even at concentrations equivalent to that of substrate. Most significant, however, is its attainment of a rate maximum in both benzene and THF.[22] Combined with its high specific activity, this observation suggests that this multidentate ligand possesses enough donor sites in one molecule to provide maximum solvation (*i.e.*, a further increase in crown ether concentration results in no increase in cation solvation).[23] In other words, the monosolvated ion pair **3** is the reactive species in the crown ether catalyzed reactions.[24]

Finally, it is tempting to suggest that the two ion pairs **3** and **4** may be, respectively, solvated contact ion pair and solvent-separated ion pair. However, recent spectral studies of alkali-metal salts of 1,3-diphenylbutene-1 have provided evidence for the existence, in weak solvating agents, of two distinct contact ion pairs in different solvation states.[25] Thus, **3** and **4** both could be contact ion pairs, with **4** having a larger interionic distance, but not large enough to accommodate a solvent molecule between the ions.

(18) The unsubstituted diethyl malonate rather than the *n*-butyl derivative was chosen for this study so that the remaining α hydrogen in the corresponding salt, being directly attached to the delocalized system, would be most sensitive to changes in electron density near the anion. Thus, for example, the cation effect on the α H in going from 1 to 2 is −0.08 ppm. The same effect on the $-OCH_2-$ group is −0.05 ppm, and on the C methyls only −0.02 ppm.

(19) Free ions are, of course, present in DMF solutions of sodiomalonates. At 25°, the molar conductance of diethyl sodio-*n*-butylmalonate (0.01 *M* in DMF) is 5.36. That of sodio-3-phenyl-2-benzofuranone, however, is higher by nearly one order ($\Lambda^{25°}_{0.1\ M} = 51.7$). In DME the conductance of both salts is still detectable, but in benzene neither salt conducts.

(20) Compare R. L. Buckson and S. G. Smith, *J. Phys. Chem.*, **68**, 1875 (1964).

(21) There is no experimental evidence to suggest that **3** is a discrete monosolvate and **4** is a pure disolvate. Digits are used merely to simplify the discussion.

(22) A. M. Grotens, J. Smid, and E. de Boer, *Chem. Commun.*, 759 (1971), using nmr line width studies of ^{23}Na, have found that crown ethers readily replace THF in the cationic solvation shell of $Na^+B^-(C_6H_5)_4$ in THF solution.

(23) Although the larger alkali cations are able to accommodate more than one molecule of crown ether, Pederson[8] found that crystalline complexes of sodium salts generally consist of a 1:1 ratio of polyether to salt.

(24) This means that, for crown ether, there should be a quantitative correlation between the rate acceleration and sedimentation behavior.[1] Unfortunately, attempted determination of the micelle–monomer ratio (*i.e.*, **1**:**3**) in benzene–crown ether mixtures gave results that were too poorly reproducible to be useful.

(25) J. W. Burley and R. N. Young, *J. Chem. Soc. B*, 1018 (1971).

Registry No.—Lithio diethyl malonate, 34727-00-9; diethyl sodio-*n*-butylmalonate, 22600-93-7; sodio-3-phenyl-2-benzofuranone, 34727-02-1; *n*-butyl bromide, 109-65-9; sodio diethyl malonate, 18424-75-4; lithio-3-phenyl-2-benzofuranone, 34727-03-2; lithium *p*-cresolate, 1121-69-3; sodium *p*-cresolate, 1121-70-6; lithium *p*-nitrophenolate, 1124-32-9; sodium *p*-nitrophenolate, 824-78-2.

Specific Solvent Effects. VIII. The Solvation of Sodiomalonate Ion Pairs by the Tertiary Amide Group

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The rate of alkylation of sodio *n*-butylmalonate with *n*-butyl bromide has been used to probe the mechanism of ion-pair solvation by the tertiary amide function. Changes in catalytic effect produced by varying the distance between two amide groups in the same molecule have been measured. Mutual assistance of the two groups is observed for separations of 4 and 5 carbon atoms (adipamide and pimelamide), but smaller separations (*i.e.*, glutaramide, succinamide, and oxamide) result in mutual hindrance of ion-pair solvation. These findings are consistent with the view that the tertiary amide function solvates the sodium ion by a π-donor mechanism and that, when two such groups are a proper distance apart, intramolecular disolvation of the cation can occur by such a mechanism.

The distinctly superior catalytic action of 1,2-dimethoxyethane (DME) over tetrahydrofuran (THF) and certain geometrically constrained diethers (*e.g.*, 1,3-dioxolane and 1,4-dioxane) in accelerating the alkylation of sodio diethyl *n*-butylmalonate in benzene solution was interpreted[1] in terms of selective cation solvation resulting from the bidentate donor character of DME. This view was reinforced by the observation that the hexadentate donor, dicyclohexyl-18-crown-6 polyether, is vastly more effective than DME.[2] Also explained in terms of selective cation solvation was the marked acceleration caused by the addition of small amounts of N,N-disubstituted amides and certain *P*-, *S*-, and *N*-oxides.[1,3] Evidence indicated[3] that these substances act as π donors for the cation in the same way that the polyethers serve as n donors.

Work described in the preceding papers[2,4] strongly suggested that the alkylation of sodio diethyl *n*-butylmalonate in benzene–dimethylformamide (DMF) media is a process involving an ion-pair species containing a sodium ion that is at least disolvated. This, together with the observed increased effectiveness of the multidentate ethers, leads to the prediction that certain diamides structurally permitted to disolvate the cation by an intramolecular π-donor mechanism should accelerate the alkylation more effectively than either monamides or diamides unable to undergo bidentate π interaction with the cation. To check this prediction, the effect of a series of diamides on the alkylation rate is examined in the present work. The distance between the two amide functions is varied systematically, and rate comparisons are made with the monoamide, *N*,*N*-dimethylacetamide, serving as a standard.

Because these amides are more polar than the ethers studied previously,[1,2] the dielectric constants of several benzene–amide mixtures were measured to check any possible correlation of this bulk solvent effect with corresponding rate accelerations.

Experimental Section

Materials.—Hexamethylphosphoramide (Monsanto) was purified by distillation, bp 121° (19 mm), n^{25}D 1.4570. The *N*,*N*,*N*^{1},*N*^{1}-tetramethyldiamides of the following acids were prepared according to published procedures: oxalic,[5] mp 78–80°; dimethylmalonic,[6] mp 79–80.5; succinic,[5] mp 83.5–84.5°; glutaric,[7] mp 45–47°; adipic,[5] mp 82–83°; pimelic,[6] bp 162–166° (0.7 mm), n^{25}D 1.4828; phthalic,[8,9] mp 121–123°; isophthalic,[9] mp 135–136°. Specifications for the other reagents used in this work are listed in the preceding paper.

Kinetics.—Rate measurements were conducted as described in the preceding paper.[2] Log–log plots of additive concentration *vs.* rate were statistically analyzed to determine the slopes (*i.e.*, kinetic orders of participation) of the lines and their standard deviations from linearity.

Dielectric Measurements.—Dielectric constants were measured at 25° and at a frequency of 2 MHz, using a Model 3A dielectric constant meter of the Yellow Springs Instrument Co., Inc., Yellow Springs, Ohio. Benzene ($\epsilon_{25°}$ 2.3) was used as a standard.

Results

Figure 1 shows the log–log plots of the alkylation rate *vs.* amide group concentration in benzene for six homologous diamides determined in the present work, and for acetamide, which was previously measured.[10] For the diamides, amide group concentrations, [CON(CH$_3$)$_2$], are equal to twice the molar concentrations, and for acetamide the two factors are obviously equal. From the equation (Figure 1), the empirical kinetic order of additive participation, *n*, is given by the slope of the log–log plot. The numerical *n* values also are listed in Figure 1.

The seven amides of Figure 1 can be divided into three groups of participation orders: $n = 0.8$, 1.1, and 1.4. These results are consistent with previous measurements carried out in this concentration range.[1,10] It was found that, among a number of miscellaneous addi-

(1) H. E. Zaugg, *J. Amer. Chem. Soc.*, **83**, 837 (1961); part IV in the series "Specific Solvent Effects."

(2) H. E. Zaugg, J. F. Ratajczyk, J. E. Leonard, and A. D. Schaefer, *J. Org. Chem.*, **37**, 2249 (1972).

(3) H. E. Zaugg, *J. Amer. Chem. Soc.*, **82**, 2903 (1960).

(4) G. H. Barlow and H. E. Zaugg, *J. Org. Chem.*, **37**, 2246 (1972).

(5) J. K. Lawson, Jr., and J. T. Croom, *ibid.*, **28**, 232 (1963).

(6) A. P. N. Franchimont, *Recl. Trav. Chim. Pay-Bas*, **4**, 208 (1885); Beilstein, **4**, 63.

(7) P. A. Meerburg, *ibid.*, **18**, 374 (1899); *Beilstein*, **4**, 63.

(8) J. v. Braun and W. Kaiser, *Ber.*, **55**, 1305 (1922).

(9) H. B. Kostenbauder and T. Higuchi, *J. Amer. Pharm. Ass.*, **45**, 518 (1956).

(10) H. E. Zaugg, B. W. Horrom, and S. Borgwardt, *J. Amer. Chem. Soc.*, **82**, 2895 (1960).

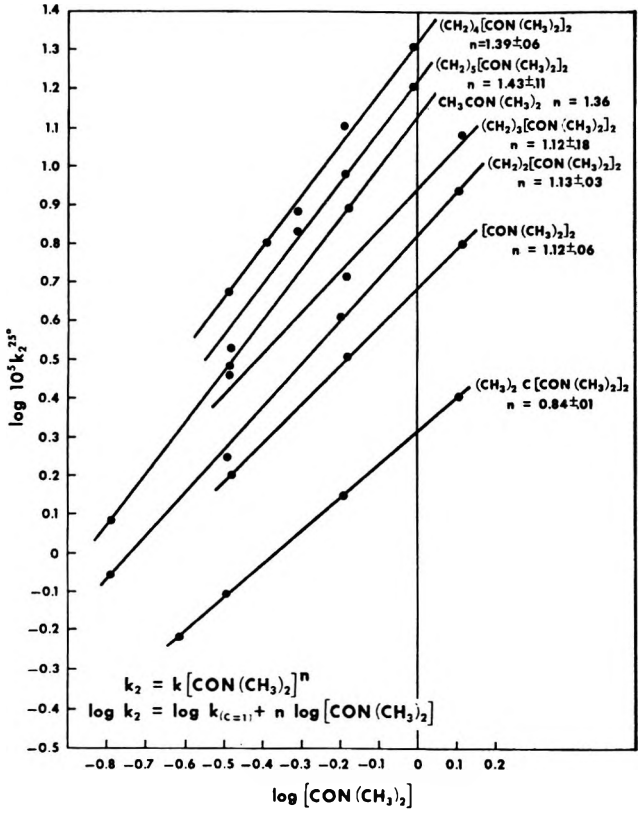

Figure 1.—Log–log plots of the rate of alkylation at 25° of diethyl sodio-*n*-butylmalonate with *n*-butyl bromide *vs.* the amide group concentration in benzene of six diamides and acetamide. (The horizontal base line at −0.5 represents the rate in the absence of amide.)

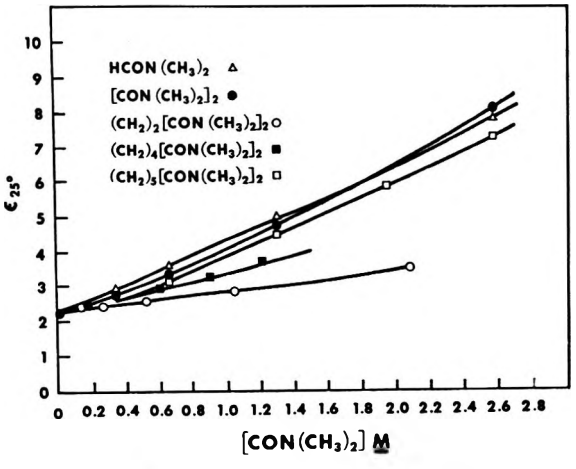

Figure 2.—Dielectric constant at 25° *vs.* concentration of amide group in benzene of one monoamide and four diamides.

tives in benzene, relatively ineffective examples (*e.g.*, acetone, pyridine, nitrobenzene, THF) showed fractional *n* values, moderately active ones (*e.g.*, DME, ethanol) gave roughly unit orders of participation, and the best ones (*e.g.*, DMSO and many N,N-disubstituted amides) had *n* values in the range 1.3 to 1.5.[11]

Because of the inequality of participation orders in the present work, valid comparisons of catalytic activity must be made at the *y* intercept of Figure 1 (*i.e.*, *n* log $[CON(CH_3)_2]$ = 0). It is apparent that activity in the series of diamides increases with increasing distance between the polar groups to an optimum separation of four carbon atoms. Anything less than this results in activity lower than that of the reference compound, but a five-atom separation still provides for augmented activity.[12,13]

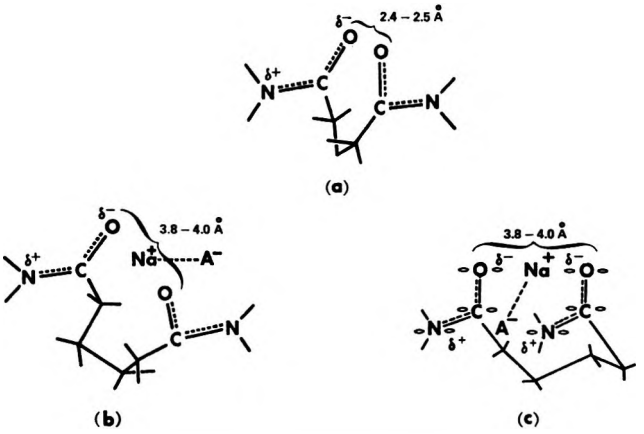

Figure 3.—Plane-parallel conformations for maximum separation of the amide groups in glutaramide (a) and adipamide (b, c).

Figure 2 illustrates the increase in dielectric constant with increasing amide group concentration in benzene for four of the diamides studied kinetically, and for DMF used as a reference. The concentration range encompasses that of the kinetic work, and once again for the diamides amide group concentrations are twice the molar concentrations. It is apparent that the first and last members of the diamide series behave most nearly like the reference amide. The other two, including the catalytically most active diamide, deviate significantly from the standard, both showing lower than normal dielectric constants.

Discussion

It is apparent from Figures 1 and 2 that there is no correlation between the dielectric constant of the medium and the corresponding alkylation rate. This is consistent with the long-held view[1,3,10] that the rate accelerations are produced through a specific solvation mechanism. Furthermore, in accord with prediction, a synergism is observed when two amide groups are a correct distance apart in the same molecule. The 4–5 carbon-atom separation required for optimum activity can be rationalized with the aid of Figure 3.

It is assumed that, to attain maximum π-donor capacity for both oxygen atoms simultaneously, their π orbitals must be directed collinearly toward a single, central sodium ion. A Dreiding model of glutaramide (Figure 3a) in this required conformation reveals that the maximum attainable distance between oxygen

(11) DMF is almost identical with *N,N*-dimethylacetamide with respect to catalytic activity (see Figure 1 of the preceding paper). Also, hexamethylphosphoramide, $[(CH_3)_2N]_3PO$, a solvent receiving considerable recent attention, was found[10] to be the best catalyst of all at 0.32 *M* concentrations. Its participation order, measured in the present work, is 1.37 ± 0.09.

(12) For obvious reasons, the unsubstituted malonamide could not be used as a chemically inert additive. The reason for the extremely poor catalytic activity of its dimethyl derivative is probably steric in nature. *N,N*-Dimethylpivalamide, for example, was found to be only half as active as dimethylacetamide.[10]

(13) *N,N,N*^{1},*N*^{1}-Tetramethylphthalic and isophthalic amides also were studied in the present work. Both gave *n* values and intercepts nearly identical with those of tetramethyloxamide.

centers is 2.4–2.5 Å.[14] It is our contention that, considering the space occupied by the extended oxygen π orbitals possessing the bulk of the electron density, this is not a sufficient separation[15] to accommodate a sodium ion (diameter 1.90 Å). A similar model for adipamide (Figure 3b) gives a maximum distance between oxygens of 3.8–4.0 Å with enough flexibility in the carbon chain to adjust downward to whatever minimum-energy dimension is required by the cation. The even greater distance afforded by the pimelamide provides no further advantage, since the optimum has been reached in the adipamide. Indeed, the larger number of conformational degrees of freedom in the pimelamide results in a less favorable entropy for disolvation so that its activity decreases with respect to the adipamide. Presumably, further chain extension would provide even less intramolecular synergism, and catalytic activity would approach that of *N,N*-dimethylacetamide.

An alternate mechanism involving intramolecular π-donor–π-acceptor solvation of both ions of the ion pair (Figure 3c) is not considered to be important for three reasons: (1) it is not likely that the steric demands for simultaneous and optimal solvation of both a small cation and a large anion could be met by any such scheme; (2) in fact, it is known[17] that dipolar aprotic compounds usually coordinate with small cations more readily than with anions; and (3) the anion in such a solvated ion pair would not possess greatly increased nucleophilic reactivity, because any decrease in sodium-ion influence would be offset by the proximity of the two positively charged nitrogen atoms.

The low activity of the other diamides compared to the standard monoamide shows that the second amide group is actually counterproductive with respect to cation solvation. Part of this effect, especially for the lower homologs, may be steric.[12] However, the abnormally low dielectric constant for the succinamide (Figure 2) suggests the occurrence of considerable intramolecular neutralization of the amide dipoles. This would tend to reduce the π-donor capacity of either amide function below that of the monoamides in which such interaction occurs only through intermolecular association. The highly active adipamide also shows some evidence of such intramolecular amide interaction. In the presence of sodium ion, however, the capacity of the two functions to act synergistically (*cf.* Figure 3b) clearly supplants the deactivating effect of the dipole neutralization.

Registry No.—$HCON(CH_3)_2$, 68-12-3; $[CON(CH_3)_2]_2$, 1608-14-6; $(CH_2)_2[CON(CH_3)_2]_2$, 7334-51-2; $(CH_2)_4[CON(CH_3)_2]_2$, 3644-93-7; $(CH_2)_5[CON(CH_3)_2]_2$, 34712-64-6; diethyl *n*-butylsodiomalonate, 22600-93-7; *n*-butyl bromide, 109-65-9.

(14) A similar model of succinamide shows that the collinear requirement cannot be met.

(15) Although the "hole" in dicyclohexyl-18-crown-6 polyether is not much larger than this (2.6–3.2 Å),[16] the space occupied by the oxygen n orbitals in ethers is considerably less than that required by the π orbitals in amides.

(16) C. J. Pedersen, *J. Amer. Chem. Soc.*, **92**, 386 (1970).

(17) A. J. Parker, *Quart. Rev., Chem. Soc.*, **16**, 163 (1962).

Thermal Reactions of Alkyl Isocyanates. I

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The gas-phase thermal reactions of alkyl isocyanates have been investigated using a static manometric technique. While the ethyl compound decomposes through a complex and partly heterogeneous series of reactions, isopropyl and *tert*-butyl isocyanates yield isocyanic acid and olefins by a well-defined, homogeneous, first-order process. The effect of temperature on the rate constants is given by the following equations: isopropyl isocyanate, $\log k_1$ (sec^{-1}) = 12.71 − (53,300/2.30RT); *tert*-butyl isocyanate, $\log k_1$ (sec^{-1}) = 13.59 − (52,400/2.30RT). The results are discussed with special reference to those for alkyl isothiocyanates. It is found that substitution of sulfur by oxygen in these species results in a decrease in reactivity of three orders of magnitude. The transition state for these reactions is regarded as a six-centered structure of moderate polarity.

The results previously obtained with isothiocyanates[1] have prompted us to investigate the thermal reactions of organic isocyanates in the gas phase. The most relevant work in this field has been that of Back, *et al.*, on the photolysis[2] and the pyrolysis[3] of isocyanic acid itself at temperatures above 550°. These authors conclude that the thermal decomposition of isocyanic acid occurs through a complex mechanism of appreciable heterogeneous character. Preliminary experiments carried out in these laboratories on ethyl isocyanate between 440 and 500° showed that this, too, is a complex reaction of no well-defined stoichiometry and which is presumably heterogeneous to a large extent. The situation is complicated by the tendency of this compound to polymerize in the liquid state through a reaction which appears to be catalyzed by traces of a variety of substances, among which are the products of the pyrolysis. On the other hand, isopropyl and *tert*-butyl isocyanates decompose in carbon-coated vessels in a much simpler manner. The purpose of this work is to investigate this last reaction and to compare the results with those from the sulfur analogs, namely, alkyl isothiocyanates, in an attempt to draw general conclusions about the mechanism of elimination of pseudohalides of type RXCY (X,Y = O,S,N).

Results

Isopropyl Isocyanate.—When the pyrolysis occurs in a clean Pyrex reaction vessel, the initial rate of pressure increase was erratic, and CH_4, CO, and CO_2

(1) (a) N. Barroeta, Ph.D. Thesis, University of London, 1968; (b) N. Barroeta, A. Maccoll, and A. Fava, *J. Chem. Soc.*, 347 (1969).

(2) R. Back and R. Ketcheson, *Can. J. Chem.*, **46**, 531 (1968), and references therein.

(3) R. Back and J. Childs, *ibid.*, **46**, 1023 (1968).

were detected in the products. If the reaction vessel was "seasoned" by the allyl bromide technique, followed by repeated pyrolysis of isopropyl isocyanate, a gradual suppression of these gases was achieved and the initial rate attained a reproducible value. The initial behavior could, however, be restored by admission of air into the vessel, although this "memory effect" was lost after four or five runs.

In a well-coated vessel the stoichiometry reduces to the simple form shown in eq 1. Confirmation for

$$(CH_3)_2CHNCO \xrightarrow{k_1} HNCO + CH_3CH{=}CH_2 \qquad (1)$$

this was achieved in three ways. (a) An increase in the total pressure to a maximum value of twice the initial pressure was observed. (b) Careful analysis of the reaction mixture showed that isocyanic acid and propylene were the only products present in detectable quantities. The ir spectrum of the acid produced corresponds completely to that of isocyanic acid as reported by Herzberg and Reid.[4,5] (c) The proposed stoichiometry corresponds to the experimentally determined amounts of reaction products (Table I).

TABLE I

PRODUCT ANALYSIS IN THE PYROLYSIS OF ISOPROPYL ISOCYANATE

Compound analyzed	Temp, °C	% reaction from pressure	% reaction from direct analysis
i-C_3H_7NCO	413.0	8.7	11.1[a]
	413.0	20.7	23.1[a]
	413.0	26.9	26.3[a]
Propylene	413.0	10.4	8.9[b]
	413.0	18.9	19.0[b]
	413.0	24.7	22.8[b]
	413.0	33.3	32.0[b]
	440.8	14.8	14.5[c]
	440.8	25.6	25.4[c]
	440.8	39.5	37.4[c]
	440.8	42.2	49.0[c]
	440.8	57.7	56.5[c]
	440.8	70.1	69.3[c]
	440.8	86.1	85.1[c]
	480.4	50.8	50.5[c]
	480.4	58.8	57.4[c]
	480.4	64.2	65.4[c]

[a] By method A. [b] By method B. [c] By method C.

Kinetics.—For runs made in nonseasoned vessels, the initial rate is large (Table II), relative to those runs made in perfectly coated ones, and the first-order rate constant falls steadily with time. This behavior is related to the fact that values of $\Delta P_{total}/P_{propylene}$ of the order of 1.30 were observed and, on the whole, indicates that a complex heterogeneous reaction, probably involving both isocyanic acid and isopropyl isocyanate, is set up. To overcome these difficulties the kinetic study was carried out in a reactor having a surface to volume ratio of 0.8 cm^{-1} and which had been seasoned previously by repeated pyrolysis of isopropyl isocyanate. Under these conditions the production of permanent gases was suppressed and all heterogeneous processes were reduced to a negligible extent as can be ascertained from Table II. The first-order nature of the reaction follows from the observed proportionality between initial velocity (V_0) and initial pressure of reactant (P_0). According to this relationship the first-order-rate constants (Table III) were calculated as

$$-k_1 = t^{-1} \ln|(2P_0 - P)/P_0|$$

TABLE II

EFFECT OF SURFACE ON REACTION VELOCITY FOR C_3H_7NCO

Temp, °C	A/V, cm^{-1}	Reactor's surface	$k_1^{exp} \times 10^4$ sec^{-1}	$k_1^{calcd} \times 10^4$ sec^{-1} [a]
413.5	4.0	Clean	4.07	0.538
413.5	4.0	Coated	1.78	0.538
426.5	4.0	Coated	1.37	1.16
447.1	4.0	Coated	4.41	3.46
459.0	4.0	Coated	7.50	6.52
471.0	4.0	Coated	13.00	11.4
484.0	4.0	Coated	19.6	21.1

[a] By calculated rate constant (k_1^{calcd}) is meant the value computed from the Arrhenius equation obtained when the reaction is studied in a "coated vessel" with a surface to volume ratio of 0.80 cm^{-1}.

TABLE III

FIRST-ORDER RATE CONSTANTS AT VARYING INITIAL PRESSURES

Temp, °C	P_0 of C_3H_7NCO, mm	$k_1 \times 10^4$ sec^{-1}
440.8	132	2.66
440.8	166	2.62
440.8	180	2.40
440.8	239	2.43
440.8	434	2.73
498.1	70	39.3
498.1	145	40.2
498.1	190	38.8
498.1	240	37.2

To check on the possibility of chain mechanisms, rate constants were determined from runs to which a variety of radical chain inhibitors were added, but only a very small decrease in rate was observed and this was apparently not connected with the relative amount of inhibitor used (Table IV).

TABLE IV

EFFECT OF INHIBITORS ON REACTION VELOCITY IN THE PYROLYSIS OF ISOPROPYL ISOCYANATE

Inhibitor	% inhibitor	Temp, °C	k_1^{found}/k_1^{calcd}	k_1^{found}/k_1^{none} [a]
Nitric oxide	22.2	425.8	0.937	0.981
	21.3	467.0	0.922	0.873
	24.6	467.0	1.06	1.01
Propylene	68.6	440.8	0.936	0.915
	113.4	440.8	0.930	0.909
	42.8	467.0	0.902	0.855
	58.2	467.0	0.996	0.944
	94.6	467.0	0.932	0.883
	39.4	480.4	0.897	1.05
	85.5	480.4	0.855	1.00
Cyclohexene	72.2	464.0	0.936	
trans-Butene-2	75.0	464.0	0.881	

[a] Experimental value of k_1 for the unperturbed reaction: none = no additive. These runs were made from the same sample of isocyanate and immediately before the inhibition experiments and thus give an idea of the reproducibility of the rate constants through a comparison between k_1^{calcd} and k_1^{none}.

(4) C. Reid, *J. Chem. Phys.*, **18**, 1544 (1950).
(5) G. Herzberg and C. Reid, *Trans. Faraday Soc.*, **46**, 92 (1950).

The results of pyrolysis at seven temperatures within the range of 425–498° and an average of five runs at each temperature were treated by a least-squares procedure to yield the Arrhenius equation

$$\log k_1\ (\text{sec}^{-1}) = 12.71 \pm 0.24 - \frac{53{,}290 \pm 800}{2.303RT}$$

tert-Butyl Isocyanate. Stoichiometry.—When the thermolysis was carried out in a clean Pyrex glass reactor the occurrence of heterogeneous reactions led to irreproducibility in the rate constants, formation of permanent gases (although to a lesser extent than in the isopropyl isocyanate pyrolysis), and a marked decrease with time of the total pressure after it had attained a maximum value of $\sim 1.6P_0$. All of these complications disappeared when the reactor was conditioned by repeated pyrolysis of *tert*-butyl isocyanate itself. The remaining reaction can be presented remarkably well by eq 2 as was demonstrated by careful

$$(CH_3)_3CNCO \xrightarrow{k_1} (CH_3)_2C{=}CH_2 + HNCO \qquad (2)$$

analysis of the reaction mixture. In Table V the extent of the reaction as given by pressure measurements

TABLE V
VALIDITY OF PRESSURE READINGS AS A MEASURE OF THE EXTENT OF REACTION IN THE PYROLYSIS OF *tert*-BUTYL ISOCYANATE

Compound analyzed	Temp, °C	% reaction from pressure	% reaction from direct analysis	
			Method A	Method B
2-Methylpropene	410.0	23.0		23.2
	410.0	35.6		34.3
	410.0	55.3		54.7
	410.0	72.2		70.1
	410.0	86.0		86.5
	410.0	96.0		94.2
tert-Butyl isocyanate	400.0	22.9	24.4	
	410.0	9.0	9.1	
	410.0	19.6	19.9	
	410.0	31.3	31.9	
	410.0	45.4	48.0	
	420.0	28.9	27.5	
	420.0	43.9	46.0	
	420.0	50.7	50.6	

is compared with the same quantity calculated from direct determination of the reaction products.

A further test on the stoichiometry was performed by titration of the total isocyanate (*tert*-butyl isocyanate plus isocyanic acid) present in the reaction mixture with *tert*-butylamine according to Wild's method.[6] This should give 100% relative to the initial pressure. The mean value of 14 determinations distributed within the first half-life of the reaction was 100.0 ± 1.6, thus confirming reaction 2.

Kinetics.—The total pressure increase followed the first-order rate law until the reaction was at least 50% complete and this equation was used to calculate first-order rate constants. No trend was observed when the initial concentration was varied by a factor of 13.

Attempts to modify the value of the rate constant by increasing the surface to volume ratio of the reactor by a factor of 4 were unsuccessful as was the addition of propene and cyclohexene in amounts as high as 120%.

The temperature dependence of the rate constant was found to obey the Arrhenius equation

$$\log k_1\ (\text{sec}^{-1}) = 13.59 \pm 0.29 - \frac{52{,}380 \pm 540}{2.303\ RT}$$

This equation was obtained by the least-squares method from experiments made at nine temperatures within the interval of 380–440°.

Discussion

In agreement with the pattern shown in the pyrolysis of other substances such as alkyl halides and esters, the complexity of these reactions greatly decreases when going from ethyl to *tert*-butyl derivatives. As explained above, heterogeneous reactions, although present when all the isocyanates were studied in clean Pyrex glass reactors, can be eliminated by properly covering the walls of the reactor with carbonaceous films arising from the pyrolysis of isocyanates themselves. An exception to this was the pyrolysis of ethyl isocyanate which is complex under any condition. On the other hand, we believe that the results of the experiments in which the nature and extent of reactor's surface was varied are sufficient evidence of homogeneous mechanism in the cases of isopropyl and *tert*-butyl isocyanates. We further propose that these latter reactions are unimolecular eliminations. The evidence for this comes from a consideration of several facts which can be summarized as follows. In the first place, the reactions obey a first-order kinetic law. Secondly, the increase in total pressure follows a well-defined, exponential form with no observable induction periods. Thirdly, a careful analysis of the products reveals an uncomplicated stoichiometry. A radical chain reaction would yield detectable amounts of by-products unless the chain length is very large, and the isocyanate radical is not expected to propagate such chains. Fourthly, the reactions are not significantly affected, either in the rate or in the distribution of products by the addition of well-known inhibiting substances like propene, cyclohexene, and nitric oxide. Finally, the experimental Arrhenius parameters are better understood in terms of a molecular split into isocyanic acid and olefin. If a radical nonchain mechanism with the homolytic breakage of the C–N bond as the rate-controlling step were operating, one would expect a larger A factor and an activation energy equal or higher than the dissociation energy of that bond. Although no direct measure of this quantity has been published one can make a reasonable estimate on two different grounds. Firstly, if one accept 100 kcal/mol as the lower limit for the H–NCO bond[7] one can easily work out a lower limit of 73 ± 3 kcal/mol for the C–N bond in methyl and ethyl isocyanates through enthalpies of formation of molecules[8] and radicals.[9] Secondly, preliminary work on electron-impact phenomena on *tert*-butyl isocyanate yields a lower limit for the dissociation energy of the C–NCO bond of 74 kcal/mol *via* the appear-

(6) F. Wild, "Estimation of Organic Compounds," Cambridge University Press, Cambridge, p 201, 1953.

(7) W. D. Wooley and R. A. Back, *Can. J. Chem.*, **46**, 295 (1968).

(8) D. R. Stull, E. F. Westrum, Jr., and G. C. Sinke, "The Chemical Thermodynamics of Organic Compounds," Wiley, New York, N. Y., p 631, 1969.

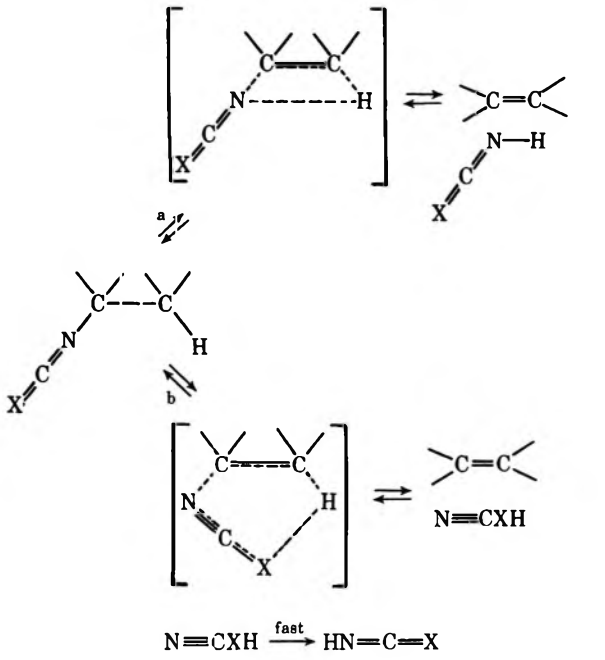
(9) D. M. Golden and S. W. Benson, *Chem. Rev.*, **69**, 125 (1969).

ance potential[10] of $C_4H_9^+$ and the ionization potential of the *tert*-butyl radical.[11] The difference between this values and the observed activation energies is far too great to be explained by the inaccuracies in the estimates so that this mechanism can be safely dismissed.

One of the reasons for studying the thermolysis of isocyanates was to investigate the effect of atomic substitution within the pseudohalogen moiety in the hope that the results could be useful when discussing the nature of the transition state of the isothiocyanate elimination reaction. We have pointed out[1] that for this reaction there exists an ambiguity about the structure of the transition state, namely, that a four-center reaction yields isothiocyanic acid directly (Scheme I, path a) or a six-center reaction initially forms thiocyanic acid which then isomerizes very rapidly to isothiocyanic acid (Scheme I, path b). We have been

SCHEME I

THE TWO POSSIBLE TRANSITION STATES FOR PSEUDOHALIDES OF ALLENIC STRUCTURE (X = S, O)



inclined to favor the former structure on steric and electronic grounds,[1,12] the problem at hand being related to that of the actual existence of species H–OCN and H–SCN in the gas phase which has been discussed by several authors.[4,5,13,14]

As pointed out above, the acid produced in the pyrolysis of isopropyl and *tert*-butyl isocyanates, as well as for thio- and isothiocyanates, was that tautomer with the hydrogen attached to nitrogen. This fact, together with the alleged[1,12] structural difficulty to "close" a six-membered ring and the availability of sp^2 unpaired electrons on nitrogen, suggest a four-center transition state, although it is now realized that a reaction which could presumably be correlated to this structure, namely, the unimolecular split of *tert*-butylamine,[15] has a much higher activation energy and this could be taken as evidence against it.

The sulfur-for-oxygen substitution is accompanied by changes in the electronic distribution with profound bearings on the reaction. One may take the atomic charges calculated by Wagner[16] for HNCS and HNCO as a first approximation to the problem. According to this charge distribution, the negative atomic charge is diminished at both ends of the isocyanate group in relation to the sulfur analogs. This could explain, at least in part, why the activation energies for the isocyanates are ~13 kcal/mol higher than for the corresponding isothiocyanates which means a factor of three orders of magnitude in the relative rates (Table VI). Because of this large difference in reactivity,

TABLE VI

RATE CONSTANTS FOR THE REACTION RX ⟶ HX + OLEFIN AT 440.8°

Reactant	$k_1 \times 10^4$, sec^{-1}	k_1 (*t*-C_4H_9X)/k_1 (*i*-C_3H_7X)	Reference
C_3H_7NCS	7346.0		16
t-C_4H_9NCS	84240.0	11.5	16
i-C_3H_7NCO	2.49		This work
t-C_4H_9NCO	36.6	14.5	This work
i-$C_3H_7OCOCH_3$	1690.0		*a*
t-$C_4H_9OCOCH_3$	81000.0	47.9	*a*
tert-Butyl-NH_2	0.0053		15

[a] Preferred value: S. W. Benson and H. E. O'Neal, "Kinetic Data on Gas Phase Unimolecular Reactions," U. S. Department of Commerce, Washington, D. C., Publication NSRDS-NBS-21, pp 169, 189, 1970.

one is inclined to conclude that the oxygen and sulfur atoms must be directly involved in the reaction center rather than acting indirectly on the nitrogen atom. This being more so when one considers that, because of the particular geometry of the π orbitals within the NCO group, the β hydrogen "does not see" the electronic changes in the orbital associated with nitrogen whereas the C–N π orbital, being at right angles to the former, is particularly suited for an initial attack on the β hydrogen and changes on this orbital should be reflected more effectively in the reactivity. This view is reinforced by the fact that a similarly large difference in reactivity exists between xanthates and carboxylic and carbonate esters where doubly bonded oxygen and sulfur abstract a β hydrogen in a six-center transition state.[17] Furthermore, in spite of the above-mentioned steric restriction, this structure is not unattainable for isothiocyanates. On the contrary, an equivalent arrangement of atoms is generally accepted for the isomerization of allylic thiocyanates.[18]

As is apparent from the discussion above, the transition state for elimination in molecules of type RNCX (X = X, O) is probably more accurately represented by a six-centered structure, contrary to our previous views,[12] although the initial interaction between the

(10) A. Maccoll, private communication.

(11) J. L. Franklin, J. G. Dillard, H. M. Rosenstock, J. T. Herron, K. Draxl, and F. H. Field, U. S. Department of Commerce, Washington, D. C., Publication NSRDS-NBS 26, p 14, 1969.

(12) N. Barroeta, A. Maccoll, M. Cavazza, L. Congiu, and A. Fava, *J. Chem. Soc.*, 1267 (1971).

(13) N. Groving and A. Holm, *Acta Chem. Scand.*, **19**, 1768 (1965).

(14) C. I. Beard and B. P. Dailey, *J. Chem. Phys.*, **15**,762 (1947).

(15) H. O. Pritchard, R. G. Sowden, and A. I. Trotman-Dickenson, *J. Chem. Soc.*, 546 (1954).

(16) E. L. Wagner, *J. Chem. Phys.*, **43**, 2728 (1965).

(17) C. H. De Puy and R. W. King, *Chem. Rev.*, **60**, 431 (1960).

(18) A. Fava in "The Chemistry of Sulfur Compounds," N. Kharash and C. Meyers, Ed., Pergamon Press, Oxford, p 73, 1966.

hydrogen and the -NCX group could be through the π orbitals of the C=X bond. However, this formulation leaves unanswered the fact that only HNCO and HNCS are detected in the products, although under the conditions of our analysis, namely, at least 25% decomposition and in a 10-cm ir gas cell, this could be accounted for if the rate constant of isomerization of these species is at least twenty times larger as that for elimination. We plan to do more work along these lines and to extend the investigation to the isoselenocyanates.

An indication of the degree of polarity of the reaction is obtained from Table VI where a similar effect of α-methylation on rate is observed for isocyanates and isothiocyanates suggesting identity of mechanism. The absolute magnitude of this effect, although comparable with that found in the acetates, is much less than in the case of alkyl halides, a reaction regarded as quasiheterolytic.[19]

Experimental Section

An all-glass apparatus of conventional design was used. The reaction vessel was a cylinder of about 380-ml capacity and fitted with a glass-diaphragm gauge which allowed the kinetics to be followed manometrically. The temperature of the furnance was kept constant within 0.2° by means of an RT5 Mk.2 temperature controller from Associated Electrical Industries, England.

Reagents.—Isopropyl and *tert*-butyl isocyanates were laboratory reagents from K & K Laboratories, Inc., that had been fractionated to give a purity better than 99.9% as established by gas chromatography using a flame ionisation detector.

Quantitative Analysis.—Method A was used for determination of the starting material by the internal standard technique. The reaction mixture was condensed, at liquid nitrogen temperature, directly in a trap containing a known amount of the standard. For this purpose, *n*-heptane and toluene were used for the determination of isopropyl and *tert*-butyl isocyanates, respectively. The factors used to convert chromatographic area ratios into pressure ratios were found to be 3.17 ± 0.15 and 1.92 ± 0.09 for the flame ionisation detector.

Method B was used for the analysis of olefins. The reaction mixture was removed from the reactor and passed through a column filled with soda-lime followed by a trap at −80°. The olefin was finally condensed at liquid nitrogen temperature in a bulb containing the standard. Isobutylene and propylene were determined in this manner with *n*-butane as a standard. The calibration factors were 0.934 ± 0.042 and 1.26 ± 0.07, respectively.

Method C was employed for the determination of propylene and was similar to method B except that the final bulb was calibrated and the amount of gas computed from P, V, and T measurements.

Instrumental Analysis.—The reaction products were identified by a combination of several physical methods of analysis which included gas chromatography with Perkin-Elmer F11 apparatus fitted with both thermal conductivity and flame ionisation detectors. For the gas chromatography–mass spectrometry technique a Perkin-Elmer 990 chromatograph coupled to a Hitachi Perkin-Elmer RMU-6H mass spectrometer was used. Ir analysis of gases were carried out in a Perkin-Elmer 337 grating spectrophotometer fitted with a 10-cm gas cell. Nmr analysis of the hydrocarbon fraction was performed at temperatures sufficiently low to keep the sample liquid in a Varian A-60 apparatus.

Registry No.—Isopropyl isocyanate, 1795-48-8; *tert*-butyl isocyanate, 1609-86-5.

(19) A. Maccoll, *Chem. Rev.*, **69**, 32 (1969).

Diquaternary Salts. I. Preparation and Characterization of the Diquaternary Salts of Some Diazines and Diazoles[1]

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By using oxonium salts as alkylating agents, diquaternary salts of pyrazines, pyrimidines, pyridazines, triazoles, and thiadiazoles have been prepared for the first time. Structures were established by a combination of spectroscopic and chemical techniques. Pyrazinium diquats were found to undergo spontaneous radical cation formation upon solution in alcohols, whereas pyrimidinium salts did not. A rationale for this in terms of HMO theory is presented.

Many monocyclic diaza aromatics, including pyrazines, pyrimidines, pyridazines, and various diazoles, possess two nitrogen atoms whose unshared electron pairs are not part of a π-electron system. While in principle, such molecules could form diquaternary salts without loss of aromaticity, in practice diquaternization has apparently never been observed.[2] Thus Bahner and Norton obtained only monoquaternary salts from the reaction of pyrazine with excess phenacyl bromide,[3] and Blood and Noller were unable to diquaternize pyridazine with *cis*-1,4-dibromo-2-butene, even though intramolecularity favored the second alkylation step.[4] Undoubtedly, these failures arise from the expected reduction in nucleophilicity of the second nitrogen attendant upon quaternization of the first. An estimate of the magnitude of this effect can be made by assuming that nucleophilicity and basicity are roughly parallel. The two K_a's of pyrazine, for example, differ by over six powers of ten.[5] A similar difference in the nucleophilicities of the dibase and of its monoquaternary salt might be expected, and therefore failure to observe diquaternization is not surprising. It seemed to us that the presence of two positive charges in a conjugated ring might be expected to lead to enhanced reactivity, and we have therefore undertaken an investigation of the preparation and properties of diquaternary salts. An additional stimulus for this work

(1) Taken in part from the Ph.D. thesis of K. S. Prasad, St. Louis University, 1970. For a preliminary communication see T. J. Curphey, *J. Amer. Chem. Soc.*, **87**, 2063 (1965).

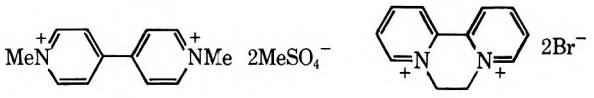
(2) For a review on quaternization of heterocycles see G. F. Duffin, *Advan. Heterocycl. Chem.*, **3**, 1 (1964).

(3) C. T. Bahner and L. L. Norton, *J. Amer. Chem. Soc.*, **72**, 2881 (1950). See also Y. T. Pratt in "Heterocyclic Compounds," Vol. 6, R. C. Elderfield, Ed., Wiley, New York, N. Y., 1957, p 400.

(4) A. E. Blood and C. R. Noller, *J. Org. Chem.*, **22**, 844 (1957).

(5) A. S. Chia and R. F. Trimble, Jr., *J. Chem. Phys.*, **65**, 863 (1961).

was the known herbicidal activity of the salts paraquat and diquat,[6] and of substances related to them.[7]



paraquat diquat

Preparation of Diquats.—Previous failures to observe dialkylation with alkyl halides led us to try the more potent trialkyloxonium salts[8] as alkylating agents. Addition of pyrazine to slightly more than 2 equiv of triethyloxonium tetrafluoroborate[9] in cold 1,2-dichloroethane produced an immediate precipitate of monoquaternary salt. Upon heating this suspension to reflux, the precipitate redissolved and highly crystalline diquat **1** began to separate from the hot mixture.[10] A further brief reaction period, cooling and filtration gave **1** in virtually quantitative yield. After determining that the reaction product from pyrazine did indeed have structure **1** (*vide infra*), we proceeded to examine diquaternization of a number of diazines and diazoles, with the results shown in Table I. While

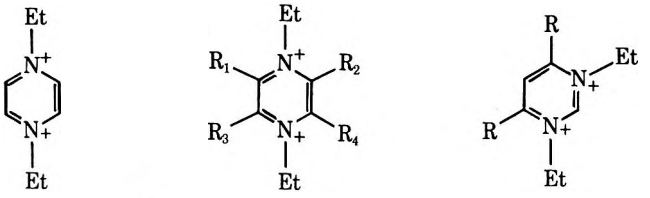
TABLE I

PREPARATION OF DIQUATERNARY SALTS[a]

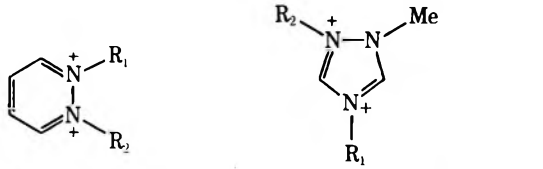
Expt no.	Diquat	Alkylating agent	Solvent	Yield, %
1	1	$Et_3O^+BF_4^-$	$ClCH_2CH_2Cl$	97
2	1	$(EtO)_2CH^+BF_4^-$	$ClCH_2CH_2Cl$	85
3	2a	$Et_3O^+BF_4^-$	$ClCH_2CH_2Cl$	95
4	2b	$Et_3O^+BF_4^-$	$ClCH_2CH_2Cl$	46[b]
5	2c	$Et_3O^+BF_4^-$	$ClCH_2CH_2Cl$	5
6	3a	$Et_3O^+BF_4^-$	$ClCH_2CH_2Cl$	99
7	3b	$Et_3O^+BF_4^-$	$ClCH_2CH_2Cl$	98
8	4a	$Me_3O^+BF_4^-$	None	21
9	4b	$Me_3O^+BF_4^-$	None	4[c]
10	5a	$Me_3O^+BF_4^-$	$ClCH_2CH_2Cl$	67
11	5a	$Me_3O^+BF_4^-$	SO_2	35
12	5a	$Me_3O^+BF_4^-$	CH_3NO_2	2
13	5a	$Me_3O^+BF_4^-$	None	65
14	5b	$Et_3O^+BF_4^-$	$ClCH_2CH_2Cl$	35
15	5b	$(EtO)_2CH^+BF_4^-$	$ClCH_2CH_2Cl$	8
16	5c	$Me_3O^+BF_4^-$	None	53[c]
17	6a	$Me_3O^+BF_4^-$	$ClCH_2CH_2Cl$	67
18	6a	$Me_3O^+BF_4^-$	None	60
19	6b	$Me_3O^+BF_4^-$	None	45[c]
20	7a	$Me_3O^+BF_4^-$	None	52
21	7b	$Me_3O^+BF_4^-$	None	17[c]

[a] In most cases 2.5 mol of alkylating agent per mole of base was used, the reaction temperature was approximately 85°, and the reaction time varied from 15 min to 1 hr. See Experimental Section for exact details. [b] Estimated by nmr analysis of the crude product, a mixture of monoquat and diquat. [c] The starting material for this alkylation was the ethyl monoquat.

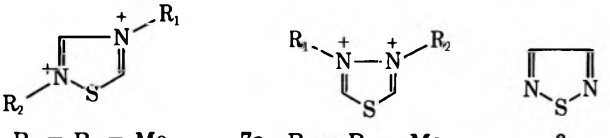
we cannot claim to have carried out an exhaustive investigation, nevertheless, several generalizations can be made as a result of these experiments. First, in common with other quaternizations, the ease of diquaternization is apparently sensitive to steric hindrance. One methyl group on an adjacent carbon had little effect (compare expt 1 to 3 and 6 to 7), but two flanking methyl groups reduced considerably the yield of diquaternary salt (compare expt 1, 4, and 5). There was also some indication that an adjacent ethyl group had an adverse effect on yield (compare expt 8 to 9 and 20 to 21). These reductions in yield are undoubtedly due in large measure to a decrease in the rate of alkylation of the more sterically hindered nitrogens, and they parallel closely the rate differences observed for quaternization of pyridines.[11] Second, in refluxing dichloroethane the effectiveness of the three alkylating agents studied was in the order $Me_3O^+BF_4^-$ > $Et_3O^+BF_4^-$ > $(EtO)_2CH^+BF_4^-$. For example,



1 **2a**, $R_1 = R_4 = Me$; $R_2 = R_3 = H$ **3a**, R = H
b, $R_1 = R_2 = Me$; $R_3 = R_4 = H$ **b**, R = Me
c, $R_1 = R_2 = R_3 = R_4 = Me$



4a, $R_1 = R_2 = Me$ **5a**, $R_1 = R_2 = Me$
b, $R_1 = Et$; $R_2 = Me$ **b**, $R_1 = R_2 = Et$
c, $R_1 = Et$; $R_2 = Me$



6a, $R_1 = R_2 = Me$ **7a**, $R_1 = R_2 = Me$ **8**
b, $R_1 = Et$; $R_2 = Me$ **b**, $R_1 = Et$; $R_2 = Me$

diquaternization of 1-methyl-1,2,4-triazole with $Me_3O^+BF_4^-$ (expt 10) gave better results than quaternization with $Et_3O^+BF_4^-$ (expt 14), and, while 1,2,4-thiadiazole was diquaternized by $Me_3O^+BF_4^-$ (expt 17), no diquat was obtained from a similar reaction with $Et_3O^+BF_4^-$. The differences between the methyl and ethyl oxonium salts are probably primarily steric in origin and parallel similar differences noted for the alkyl halides.[11] Based on work of Kabuss[12] who had demonstrated the superior electrophilicity of dialkoxycarbonium ions toward several weak nucleophiles, we briefly examined $(EtO)_2CH^+BF_4^-$ as an ethylating agent. In the two cases tried, however, this reagent gave lower yields of diquat than $Et_3O^+BF_4^-$ (expt 1, 2, and 14, 15), and we did not study it further.

Because of the limited solubility of the oxonium salt, alkylations by $Me_3O^+BF_4^-$ in dichloroethane are heterogeneous and occur either on the surface of the suspended oxonium salt or in the bulk of the solution where the concentration of the alkylating agent is low.

(6) W. R. Boon, *Chem. Ind. (London)*, 782 (1965).

(7) A. L. Black and L. A. Summers, *J. Chem. Soc. C.*, 610 (1969), and previous papers in this series; E. C. Campbell, E. E. Glover, and G. Trenholm, *ibid.*, 1987 (1969), and previous papers in this series.

(8) H. Meerwein in "Methoden der Organischen Chemie," (Houben-Weyl), Vol. 6/3, Georg Thieme Verlag, Stuttgart, 1965, p 325.

(9) H. Meerwein, *Org. Syn.*, **46**, 113 (1966).

(10) Unless otherwise indicated, the anions throughout this paper are tetrafluoroborates.

(11) Reference 2, p 11.

(12) S. Kabuss, *Angew. Chem., Int. Ed. Engl.*, **5**, 675 (1966); K. Kimroth and P. Heinrich, *ibid.*, **5**, 676 (1966); R. F. Borch, *J. Org. Chem.*, **34**, 627 (1969).

In hopes of finding a more potent alkylating system, we investigated solutions of the trimethyloxonium salt in liquid sulfur dioxide and in nitromethane (expt 11 and 12). Both of these homogeneous systems, however, proved less effective than the heterogeneous one. We then discovered that simple fusion of a base with trimethyloxonium tetrafluoroborate was in general superior to any other alkylation procedure.[13] Utiling this method we were able to achieve two dialkylations for which other methods had previously failed, dialkylation of pyridazine (expt 8 and 9) and of 1,3,4-thiadiazole (expt 20 and 21). The fusion procedure thus allowed the preparation of diquats in which, formally at least, the two positive charges were on adjacent nitrogen atoms. While some experimentation may be necessary to discover the best conditions, we regard this procedure as the one of choice for the preparation of diquats.[14] Undoubtedly, its effectiveness is due to the very high concentration of alkylating agent (and base) in the melt and to the high polarity of the reaction mixture which greatly accelerate the rate of reaction. At the moment the only base which has resisted diquaternization by any procedure is 1,2,5-thiadiazole (**8**). The monoquaternary salt of this base appeared to be somewhat unstable, however, and our failure to obtain a diquaternary salt may be due to rapid decomposition of the monoquat or diquat rather than to any failure of the dialkylation *per se*.

Structure of Diquats.—Three lines of proof were used to secure the structures of the diquats reported in this paper. First, satisfactory analytical data were obtained for almost all diquats (see Experimental Section). Second, nmr spectra fully supported the assigned structures. For example, the spectrum of diquat **1** showed a low-field singlet for the ring hydrogens, a quartet for the methylene hydrogens, and a triplet for the methyl hydrogens. The integrated intensities of the three types of hydrogens were in the expected ratios of 2:2:3. Likewise, for diquat **3a** the hydrogen at C-2 appeared at lowest field as a singlet, strongly deshielded by the two adjacent positive nitrogens. The equivalent hydrogens at C-3 and C-5 appeared as a doublet at somewhat higher field, deshielded by the single adjacent postive nitrogen, and the C-4 hydrogen appeared as a triplet at still higher field. The equivalent ethyl groups in **3a** appeared as a quartet and triplet. Again, integrated intensities were in the expected ratios. Further details of these and other nmr spectra can be found in the Experimental Section, but in every case the spectra fully supported the assigned structures.

While analytical and spectroscopic data might perhaps have sufficed, the unique nature of the diquats led us in selected cases to pursue a third line of structure proof, conversion to substances of known structure. The first diquat prepared, the pyrazine salt **1**, was reduced catalytically in good yield to the bisfluoroborate salt of 1,4-diethylpiperazine. The reduction product was identical with material prepared from 1,4-diethylpiperazine and fluoroboric acid. This conversion ruled out, for example, the rather remote possibility that one or both of the ethyl groups in **1** was attached to carbon rather than nitrogen.[15] Three other diquats were subjected to hydrolytic degradation in order to confirm their structures. A solution of the diquat in dilute sulfuric acid was first refluxed, then basified, and the liberated organic bases were isolated by steam distillation and conversion to the hydrochlorides. For separation and analysis the hydrochlorides were converted to trifluoroacetamides,[16] and the amides, after separation and purification by gas chromatography, were compared with authentic samples. By this procedure **5b** afforded approximately equal amounts of ethylamine and 1-methyl-2-ethylhydrazine.[17] In the case of diquat **5c**, which had been synthesized from 1-methyl-1,2,4-triazole by monoalkylation with $Et_3O^+BF_4^-$ followed by methylation with $Me_3O^+BF_4^-$, degradation to ethylamine and 1,2-dimethylhydrazine established that, as expected,[18] the first alkylation had taken place at N-4 rather than at N-2. In view of the fact that thiophene can be S-alkylated,[19] we had considered it barely possible that 1,3,4-thiadiazole might alkylate on sulfur rather than on nitrogen, thereby placing the two positive charges in a more favorable 1,3 relationship on the ring.[20] In fact, however, degradation of **7b** to 1-methyl-2-ethylhydrazine established that both alkylations had occurred on nitrogen.

Two structural points remain to be disposed of. Because of the failure of 1,3,4-thiadiazole to alkylate on sulfur, we believed it highly improbable that 1,2,4-thiadiazole would do so, and have assigned structures **6a** and **6b** accordingly. Moreover the nmr spectra of **6a** and **6b** show no evidence of *S*-methyl groups. The methyl singlets in **6a** and **6b** fall near δ 4.6, whereas the methyls of *S*-thiophenium salts fall near δ 3.2.[19] The placing of alkyl groups in **6b** (prepared by an ethylation–methylation sequence) is suggested by two lines of evidence. First, in studies of nuclear alkylation in the 1,2,4-thiadiazoles,[21] it has been shown that 5-amino-1,2,4-thiadiazole and 3-phenyl-5-methylthio-1,2,4-thiadiazole alkylate at N-4. However, it is somewhat difficult in these cases to assess the effect of the 5 substituent on the relative nucleophilicities of the two ring nitrogens. Second, we might expect that the 1,2,4-thiadiazoles would resemble the 1,2,4-triazoles and oxadiazoles. As discussed above,

(13) For similar observations see A. I. Kriprianov and A. I. Tolmachev, *Zh. Obshch. Khim.*, **27**, 142 (1957); A. J. Nunn and J. T. Ralph, *J. Chem. Soc. C*, 1568 (1966).

(14) For its use elsewhere in these laboratories for alkylation of weakly basic phosphonitriles see J. N. Rapko and G. Feistel, *Inorg. Chem.*, **9**, 1401 (1970).

(15) The pyrimidine diquat **3a** has also been converted to a substance unambiguously synthesized by another route. The chemistry of diquat **3a** will be reported in detail in part II of this series, and we postpone further discussion of its structure to that paper.

(16) M. Pailer and W. J. Huebsch, *Monatsh. Chem.*, **97**, 1541 (1966).

(17) The 1-methyl-2-ethylhydrazine required for this study was at the time an unreported compound. Two attempts at a simple synthesis of this hydrazine failed, and it was finally prepared from benzalazine in four steps. Further details may be found in the Experimental Section. Recently, another synthesis has been described: N. V. Khromov-Borisov and T. N. Kononova, *Probl. Poluch. Poluprod. Prom. Org. Sin., Akad. Nauk SSR, Otd. Obshch. Tekh. Khim.*, **10** (1967); *Chem. Abstr.*, **68**, 48947 (1968). Experimental details and physical data were not reported in the abstract and the original is unavailable to us. Consequently, we have been unable to compare our preparation with that of the Russian workers.

(18) Reference 2, p 35.

(19) R. M. Acheson and D. R. Harrison, *J. Chem. Soc. C*, 1764 (1970); G. C. Brumlick, A. I. Kosak, and R. Pitcher, *J. Amer. Chem. Soc.*, **86**, 5360 (1964).

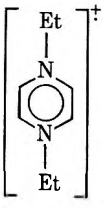
(20) Of course, this line of reasoning is somewhat naive, since one can write two entirely reasonable canonical structures for **7a** and **7b** which place a positive charge on sulfur. It is conceivable, in fact, that the sulfur atom in **7a** and **7b** carries more postive charge than either nitrogen.

(21) J. Goerdeler, A. Huppertz, and K. Weimber, *Chem. Ber.*, **87**, 68 (1954); S. Hunig and K. H. Oette, *Justus Liebigs Ann. Chem.*, **641**, 94 (1961).

the former system alkylates at N-4, and N-4 alkylation for the latter system has been demonstrated by Michelman.[22] With the structures of the alkylation products on a relatively firm basis, we turn now to observations on the properties of these diquaternary salts.

Properties of Diquats.—All of the pure diquat salts were white, usually hygroscopic, crystalline solids. However, most showed evidence of instability such as discoloration or liquefaction over a period of time. Storage at low temperature in a dry atmosphere was only partially successful in allaying this decomposition. The diquats appeared to react (heat evolution, rapid color development) with many common polar solvents, which made their purification by recrystallization difficult. For many salts solution in acetonitrile followed by immediate precipitation with dichloroethane was successful, but it was essential to work rapidly to avoid sizable losses. Acetone or methyl ethyl ketone were used for recrystallization in some cases. The only solvents in which the diquats were stable for long periods of time were trifluoroacetic acid and trifluoroacetic acid–sulfuric acid mixtures. These solvents were therefore used to obtain nmr spectra.

In examining the solubility of pyrazine diquat **1** in various solvents we observed several rather striking polychromatic displays. Addition of a small amount of **1** to water gave a transiently pink solution which almost immediately turned green, somewhat more slowly faded to violet, and then on longer standing became brown. Initially yellow solutions of **1** in methanol or ethanol turned red or violet upon standing, while yellow solutions in acetonitrile slowly developed a green coloration which eventually became a dark olive. Likewise, yellow solutions of **1** in nitromethane rapidly turned blue. Such color development led us to search for the presence of free radicals in these systems. Indeed 10^{-2} to 10^{-3} M solutions of **1** in methyl, ethyl, isopropyl, and *tert*-butyl alcohols gave a complex epr spectrum of over 200 lines, whose analysis[23] was consistent with the presence of the radical cation **9**. Pyrazine



9

diquats **2a–c** similarly gave radical cation epr spectra under these conditions. Alternatively, radical cations were formed by brief contact with granulated zinc of a solution of the diquat in trifluoroacetic acid. The dilute solutions employed in the epr studies were colorless or very faintly colored when first prepared but darkened somewhat upon long standing. However, provided that the radical cations were generated in the absence of oxygen, the epr spectra of such solutions changed only slightly over a period of many months. This suggests that color development is more likely associated with the decomposition of the radicals than, as we had originally thought, with their formation.

(22) J. S. Michelman, Ph.D. Thesis, Harvard University, 1965; *Diss. Abstr.*, **26**, 1920 (1965).

(23) M.-K. Ahn and C. S. Johnson, Jr., *Proc. Colloq. Ampere*, **14**, 253 (1966); *J. Chem. Phys.*, **50**, 632 (1969).

Formation of **9** was also demonstrated by an nmr technique. Brief contact of a trifluoroacetic acid solution of **1** in an open tube with a small piece of zinc attached to a copper wire caused all the resonance lines of **1** to broaden to the point of unobservability. On standing, however, the spectrum of **1** gradually reappeared, until after 20 min the original spectrum had been restored in slightly diminished intensity. We attribute these spectral changes to formation of a small amount of radical cation **9** upon contact with zinc. Rapid (on the nmr time scale) electron transfer between radical cation and parent dication then induces relaxation of all hydrogen nuclei and "washes out" the spectrum.[24] Destruction of the radical cation by oxygen leads finally to reappearance of the nmr spectrum.

We did note one further interesting color phenomenon. Methanol solutions of **9** when cooled in liquid nitrogen developed a bright pink coloration. Further, it has been noted that cooled solutions of the radical cations show a marked decrease in intensity of the epr spectra.[23] These observations suggest that on cooling the pyrazinium radical cations associate reversibly to give diamagnetic species. One interesting possibility is a charge transfer complex between **1** and its neutral two-electron reduction product. Similar complexes have been postulated in other systems.[25]

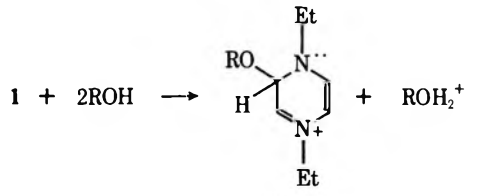
The ready one-electron reduction of the pyrazine diquats by simple alcohols no doubt reflects enhanced reactivity arising from the presence of two positive charges in a single ring. Paraquat undergoes a similar reduction, but this requires photochemical initiation and does not occur in *tert*-butyl alcohol.[26a] In hopes of shedding further light on the reduction process for the diquats, decomposition of a large quantity of **1** in isopropyl alcohol was examined. No evidence was obtained for the formation of acetone, the most likely oxidation product,[26b] although acetone was shown to be stable to the reaction conditions. Gas chromatographic analysis of a distillate from the reaction mixture showed no volatile product other than isopropyl alcohol, nor could any well-defined product be isolated from the nonvolatile portion of the reaction mixture. The formation of radical cation **9** in *tert*-butyl alcohol and the failure to find acetone as an oxidation product from isopropyl alcohol make unattractive mechanisms involving hydrogen or hydride abstraction from the oxygen or α carbon of the alcohol and suggest that the alcohol solvent may in fact function as other than a reducing agent. One possibility, for example, is a mechanism in which ROH acts as a nucleophile to initiate a redox reaction.

Addition of alcohol to diquat **1** gives an intermediate **10**, which now reduces more **1**, possibly *via* the transient 8-π-electron intermediate **11**. As written, the mechanism requires that one-third of the original diquat form **12**. However, **12** may, by a similar sequence of steps, reduce two more molecules of **1** and

(24) For the effect of radicals on nmr spectra see G. A. Webb, *Annu. Rep. NMR (Nucl. Magn. Resonance) Spectrosc.*, **3**, 211 (1970); E. de Boer and H. van Willigen, *Progr. NMR (Nucl. Magn. Resonance) Spectrosc.*, **2**, 111 (1967).

(25) H. N. Blount and T. Kuwana, *J. Amer. Chem. Soc.*, **92**, 5773 (1970), and references cited therein; T. L. Staples and M. Szwarc, *ibid.*, **92**, 5022 (1970); B. Badger and B. Brocklehurst, *Nature (London)*, **219**, 263 (1968).

(26) (a) C. S. Johnson, Jr., and H. S. Gutowsky, *J. Chem. Phys.*, **39**, 58 (1963); (b) A. S. Hopkins, A. Ledwith, and M. F. Stam, *Chem. Commun.*, 494 (1970).



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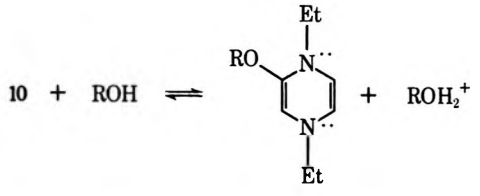

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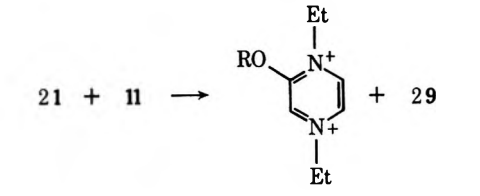

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be oxidized to a dialkoxy diquat. Ultimately, one molecule of diquat could reduce as many as eight others to the radical cation stage. The apparent anomaly of a highly electron deficient diquat functioning as a reducing agent can perhaps be resolved by realizing that the oxidation product **12** is stabilized by delocalization of one of the positive charges onto oxygen. Consequently, the overall redox reaction is energetically favorable.

We have so far been unable to observe formation of stable radical cations from alcoholic solutions of the pyrimidine diquats **3a** and **3b**. Instead, addition products analogous to **10** are formed.[27] One way of rationalizing this contrasting behavior is by resorting to simple molecular orbital calculations. A standard[28] HMO treatment of diquats **1** and **3a** with $h_N = 2$ and $k_{CN} = 1$ indicates that the energy of the lowest unoccupied MO (LUMO) of the pyrazinium diquat is 0.414β units *below* the energy of the corresponding MO in the pyrimidinium diquat. While the exact magnitude of the energy difference between LUMOs for **1** and **3a** depends on the value chosen for h_N, its direction does not.

As is well known, there is often a good linear correlation between redox potentials and LUMO energy, with a change of 1 β unit leading to a change of roughly 2 V in potential.[29] We can thus estimate that **1** should be of the order of 0.8 V more reducible than **3a**, and consequently the more facile reduction of the pyrazinium diquat is readily understood. Attempts to measure directly the difference in reduction potentials for the two diquats by electrochemical techniques have so far not been successful[30] and will not be detailed here. However, recently a similar study of the monoquaternary salts has appeared,[31] and the pyrazinium monoquat was found to be 0.27 V more reducible than the pyrimidinium monoquat. Finally, we note that the MO results for the pyridazinium dication more nearly resemble those for pyrazine than for pyrimidine. Indeed, solutions of **4a** and **4b** in water do show color changes quite similar to those of the pyrazinium diquats, but the chemistry of these pyridazinium salts remains to be elucidated. Because of the negative character of the available evidence, the mechanism by which **1** is reduced to radical cation **9** cannot be specified with absolute certainty at this time. It seems likely, however, that, whatever the mechanism for this reduction, removal of the unfavorable charge interaction in **1** must supply a large measure of the driving force for the overall change. We were encouraged by this to search for further evidence of heightened reactivity in the diquats, with results to be communicated in future papers of this series.

(27) T. J. Curphey and S. M. Kinney, unpublished work.

(28) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961, Chapter 3.

(29) (a) Reference 28, Chapter 7; (b) M. J. S. Dewar, J. A. Hashmall, and N. Trinajstic, *J. Amer. Chem. Soc.*, **92**, 5555 (1970), and references cited therein.

(30) T. R. Romer, M.S. Thesis, St. Louis University, 1966.

(31) K. B. Wiberg and T. P. Lewis, *J. Amer. Chem. Soc.*, **92**, 7154 (1970).

Experimental Section[10]

Melting points were measured in sealed evacuated capillary tubes using a Hershberg apparatus and short-range thermometers. Nmr spectra were measured on Varian Associates A-60 and HA-100 spectrometers. Infrared spectra were recorded on Perkin-Elmer Model 21 and Beckman IR-5A instruments. An Aerograph 90-P3 was used for gas chromatographic analyses. Elemental analyses were by Galbraith Laboratories, Knoxville, Tenn. Acetonitrile and DCE (1,2-dichloroethane) were dried by distillation from phosphorous pentoxide.

Preparation of Dibases.—Commercially supplied dibases were used where available. The literature synthesis of 1,2,4-thiadiazole[32] gave highly erratic results, in agreement with a report by Flexman.[33] Attempts to improve this synthesis were unrewarding. Published procedures for the preparation of 1,3,4-thiadiazole[34] and 1,2,5-thiadiazole[35] were found to be satisfactory. Reaction of methylhydrazine with the cyanuric chloride–dimethylformamide adduct, following Gold's procedure for the synthesis of 1-alkyl-1,2,4-triazoles,[36] gave 1-methyl-1,2,4-triazole in 81% yield.

Alkylation of Dibases.—Most of the diquats reported in this work were prepared by one of two general procedures, with only minor variations.

General Procedure. Method A.—A solution or suspension of 0.05 mol of alkylating agent in 20 ml of DCE was stirred under nitrogen while 0.02 mol of dibase in 5 ml of DCE was added over a 5-min period. The reaction mixture was then heated rapidly to reflux and stirred at reflux for the requisite time. Cooling to room temperature generally produced the crystalline diquat, which was filtered with minimum exposure to moisture and recrystallized as indicated.

General Procedure. Method B.—A solid mixture consisting of 2.5 mol of alkylating agent per mole of dibase was prepared in a drybox, attached to a nitrogen manifold, and heated at 85–90° (bath temperature) until it ceased evolving gas. Direct crystallization of the melt then yielded the diquat.

1,4-Diethylpyrazinium Diquat (1).—Reaction of pyrazine with triethyloxonium tetrafluoroborate by method A (35-min reflux), followed by filtration of the reaction mixture gave 1 (6.06 g, 97%), mp 204–209° dec. Solution of this material in acetonitrile, followed by slow addition with stirring of 2 volumes of DCE, led to 70% recovery of material melting at 208–210°: nmr (CF_3CO_2H, internal TMS) δ 1.92 (t, 6), 5.22 (q, 4), 9.86 ppm (s, 4).

Anal. Calcd for $C_8H_{14}N_2B_2F_8$: C, 30.82; H, 4.53; N, 8.98. Found: C, 30.55; H, 4.42; N, 8.78.

Replacing triethyloxonium tetrafluoroborate in this procedure by diethoxycarbonium tetrafluoroborate[12] lowered the yield to 85%.

(32) J. Goerdeler, J. Ohm, and O. Tegtmeyer, *Chem. Ber.*, **89**, 1534 (1956).

(33) E. A. Flexman, Jr., *Diss. Abstr.*, **28B**, 2767 (1968).

(34) B. Fohlisch, R. Braun, and K. W. Schultze, *Angew. Chem., Int. Ed. Engl.*, **6**, 361 (1967).

(35) L. M. Weinstock, *J. Org. Chem.*, **32**, 2823 (1967).

(36) H. Gold, *Angew. Chem.*, **72**, 956 (1960).

1,4-Diethyl-2,5-dimethylpyrazinium Diquat (2a).—Reaction of 2,5-dimethylpyrazine with triethyloxonium tetrafluoroborate by method A (15-min reflux) produced **2a** as a pinkish solid, mp 205–206° dec, in 95% yield. Two recrystallizations by solution in warm acetonitrile and addition of an equal volume of DCE gave pure material: mp 215–218° dec; nmr (CF_3CO_2D, external TMS) δ 1.88 (t, 6), 3.23 (s, 6), 5.05 (q, 4), 9.60 ppm (s, 2).

Anal. Calcd for $C_{10}H_{18}N_2B_2F_8$: C, 35.33; H, 5.34; N, 8.24. Found: C, 35.19; H, 5.22; N, 8.44.

1,4-Diethyl-2,6-dimethylpyrazinium Diquat (2b).—Reaction by method A of 38 g (0.2 mol) of triethyloxonium tetrafluoroborate and 2.18 g (0.02 mol) of 2,6-dimethylpyrazine in 30 ml of DCE with overnight refluxing gave an oil which solidified to a dark solid (4.50 g) upon trituration with a mixture of DCE and dry tetrahydrofuran. Nmr spectroscopy suggested that this material consisted of 60 ± 4 mol % of **2b** and 40 ± 4 mol % of monoquat (presumably the 4-ethyl isomer in which the less hindered nitrogen had been alkylated). On this basis the yield of dialkylated product was calculated to be 46%. To obtain pure **2b**, the crude salt mixture was resubmitted to alkylation exactly as described above. Now, however, the reaction mixture deposited a solid upon cooling to room temperature. The solid was precipitated three times from 1:2 acetonitrile–tetrahydrofuran to give **2b**: 1.20 g (18%); mp 153–155° dec; nmr (CF_3CO_2H, external TMS) δ 2.00 (t, 6), 3.44 (s, 6), 5.20 (q, 4), 9.65 ppm (s, 2).

Anal. Calcd for $C_{10}H_{18}N_2B_2F_8$: C, 35.33; H, 5.34; N, 8.24. Found: C, 35.20; H, 5.15; N, 8.29.

1,4-Diethyl-2,3,5,6-tetramethylpyrazinium Diquat (2c).—Alkylation of 2,3,5,6-tetramethylpyrazine with triethyloxonium tetrafluoroborate by method A (2-hr reflux) yielded 0.40 g (5%) of DCE-insoluble diquat, mp 221–226° dec. Two precipitations from acetonitrile–DCE (1:1) gave a pure sample of **2c**: mp 247–248° dec; nmr (CF_3CO_2H, internal TMS) δ 1.73 (t, 6), 3.16 (s, 12), 4.98 ppm (q, 4).

Anal. Calcd for $C_{12}H_{22}N_2B_2F_8$: C, 39.16; H, 6.03; N, 7.62. Found: C, 39.20; H, 6.18; N, 7.68.

1,3-Diethylpyrimidinium Diquat (3a).—Alkylation of pyrimidine with triethyloxonium tetrafluoroborate by method A (30-min reflux) gave 6.2 g (99%) of diquat **3a**, mp 167–172° dec. Pure material was obtained by two precipitations from 1:2 acetonitrile–DCE: mp 186–188° dec; nmr (CF_3CO_2D, internal TMS) δ 1.93 (t, 6), 5.20 (q, 4), 9.02 (t, 1), 9.93 (d, 2), 10.54 ppm (s, 1).

Anal. Calcd for $C_8H_{14}N_2B_2F_8$: C, 30.81; H, 4.52; N, 8.99. Found: C, 30.90; H, 4.67; N, 8.77.

1,3-Diethyl-4,6-dimethylpyrimidinium Diquat (3b).—Alkylation of 4,6-dimethylpyrimidine with triethyloxonium tetrafluoroborate by method A (45 minute reflux) yielded 6.60 g (98%) of **3b** as a pink solid, mp 202–207°. Two precipitations from 1:2 acetonitrile–DCE gave nearly colorless diquat: mp 212–214° dec (turns bright scarlet before melting!); nmr (CF_3CO_2D, external TMS) δ 1.75 (t, 6), 3.15 (s, 6), 4.88 (q, 4), 8.45 (s, 1), 10.10 (s, 1).

Anal. Calcd for $C_{10}H_{18}N_2B_2F_8$: C, 35.33; H, 5.34; N, 8.24. Found: C, 35.06; H, 5.28; N, 8.29.

1,2-Dimethylpyridazinium diquat (4a) was prepared by method B. A mixture of 0.77 g (5.2 mmol) of trimethyloxonium tetrafluoroborate[37] and 0.16 g (2.0 mmol) of pyridazine was held at 85–90° for 30 min. The resulting dark solid was soluble only in sulfuric acid and sulfuric–trifluoroacetic acid mixtures. It was therefore purified by several treatments with refluxing trifluoroacetic acid, leaving **4a** as a nearly white solid: 0.12 g (21%); mp 171–172° dec; nmr (3:1 CF_3CO_2D–D_2SO_4, external TMS) δ 5.10 (s, 6), 9.15 (t, 2, H-4 and H-5(?)], 10.16 ppm [t, 2, H-3 and H-6(?)].

Anal. Calcd for $C_6H_{10}N_2B_2F_8$: C, 25.40; H, 3.55; H, 9.87. Found: C, 25.28; H, 3.48; N, 9.82.

1-Ethyl-2-methylpyridazinium Diquat (4b).—Alkylation of 1.6 g (0.02 mol) of pyridazine by 3.8 g (0.02 mol) of triethyloxonium tetrafluoroborate using method A (15-min reflux) produced an oil which crystallized upon cooling to −78°. Removal of DCE solvent at −10° gave **1-ethylpyridazinium tetrafluoroborate**: 2.7 g (69%); mp 26–28°; nmr (CF_3CO_2H, internal TMS) δ 1.78 (t, 3), 4.96 (q, 2), 8.55 (m, 2), 9.50 ppm (m, 2).

Reaction of 0.95 g (5 mmol) of the above 1-ethylpyridazinium tetrafluoroborate with 0.96 g (6.5 mmol) of trimethyloxonium tetrafluoroborate by method B (45 min at 90–100°) gave **4b** as a dark solid, purified by solution in acetonitrile and precipitation with DCE: 0.06 g (4%); mp 153–154° dec; nmr (CF_3CO_2D, internal TMS) δ 1.82 (t, 3), 4.90 (s, 3), 5.22 (q, 2), 9.10 (m, 2), 10.00 (m, 2).

Anal. Calcd for $C_7H_{12}N_2B_2F_8$: C, 28.24; H, 4.03; N, 9.41. Found: C, 28.33; H, 4.10; N, 9.34.

1,2,4-Trimethyl-1,2,4-triazolium diquat (5a) was prepared by method A from 14.8 g (0.1 mol) of trimethyloxonium tetrafluoroborate and 4.15 g (0.05 mol) of 1-methyl-1,2,4-triazole in 30 ml of DCE (30 min reflux). Filtration produced nearly pure **5a**, 9.3 g (65%), mp 188–190° dec. Crystallization from acetonitrile gave pure material: mp 190–192° dec; nmr (3:1 CF_3CO_2H–H_2SO_4, external TMS) δ 4.38 (s, 3), 4.56 (s, 6), 9.98 ppm (s, 2).

Anal. Calcd for $C_5H_{11}N_3B_2F_8$: C, 20.93; H, 3.87; N, 14.65. Found: C, 21.25; H, 3.92; N, 14.66.

Replacing DCE by dry nitromethane lowered the yield to 2%.

Reaction of 1.9 g (13 mmol) of oxonium salt and 0.5 g (6 mmol) of 1-methyltriazole in 3 ml of liquid SO_2 (sealed tube) for 30 min at 80–85° followed by removal of SO_2 and trituration with acetonitrile gave 0.6 g (35%) of **5a**, mp 188–190° dec.

Fusion of the oxonium salt and the triazole by method B (80–85° for 30 min) gave **5a** in 70% yield after purification by trituration with acetonitrile.

1-Methyl-2,4-diethyl-1,2,4-triazolium Diquat (5b).—Reaction of 4.15 g (0.05 mol) of 1-methyl-1,2,4-triazole with 47.5 g (0.25 mol) of triethyloxonium salt by method A for 1 hr produced a two-phase mixture. The bottom phase was separated, washed with DCE, and dissolved in 50 ml of dry methyl ethyl ketone. Scratching this solution induced crystallization of **5b**, 5.5 g (35%), mp 94–95°. Recrystallization from 1:1 acetonitrile–methyl ethyl ketone gave the pure diquat: mp 95–96°; nmr (CF_3CO_2H–internal TMS) δ 1.75 (t, 3), 1.85 (t, 3), 4.50 (s, 3), 4.8 (apparent hextuplet arising from two overlapping quartets, 4), 10.07 ppm (s, 2).

Anal. Calcd for $C_7H_{15}N_3B_2F_8$: C, 26.71; H, 4.80; N, 13.35. Found: C, 26.74; H, 4.85; N, 13.18.

Substituting diethoxycarbonium tetrafluoroborate[12] for the triethyloxonium salt lowered the yield to 10%.

1,2-Dimethyl-4-ethyl-1,2,4-triazolium Diquat (5c).—A solution of 4.75 g (25 mmol) of triethyloxonium tetrafluoroborate and 2.1 g (25 mmol) of 1-methyl-1,2,4-triazole in 14 ml of dry dichloromethane was allowed to stand overnight and diluted with 10 ml of ether, and the precipitated **1-methyl-4-ethyl-1,2,4-triazolium tetrafluoroborate** was removed by filtration: 5.0 g (100%); mp 56–57°; nmr (CF_3CO_2H–internal TMS) δ 1.66 (t, 3), 4.20 (s, 3), 4.43 (q, 2), 8.56 (s, 1), 9.36 ppm (s, 1).

Reaction of 0.2 g (1 mmol) of the above monoquat with 0.19 g (1.3 mmol) of trimethyloxonium tetrafluoroborate by method B (80–85° for 30 min) gave **5c**, recrystallized from 1:1 acetonitrile–DCE: 0.16 g (53%); mp 141–142°; nmr (CF_3CO_2D–internal TMS) δ 1.76 (t, 3), 4.56 (s, 6), 4.74 (q, 2), 10.22 ppm (s, 2).

Anal. Calcd for $C_6H_{13}N_3B_2F_8$: C, 23.96; H, 4.36; N, 13.97. Found: C, 23.71; H, 4.33; N, 13.72.

2,4-Dimethyl-1,2,4-thiadiazolium Diquat (6a).—Alkylation of 0.86 g (10 mmol) of 1,2,4-thiadiazole by 3.7 g (25 mmol) of trimethyloxonium tetrafluoroborate using method A (1-hr reflux) followed by dilution of the oily bottom phase of the reaction mixture with trifluoroacetic acid, gave the highly insoluble **6a**: 1.74 g (60%); mp 170–172° dec; nmr (3:1 CF_3CO_2H–H_2SO_4, external TMS) δ 4.58 (s, 3), 4.64 (s, 3), 10.10 ppm (s, 1). The resonance for the remaining ring proton was apparently under the solvent peak at δ 11.05. A completely satisfactory elemental analysis for **6a** could not be obtained.

Anal. Calcd for $C_4H_8N_2SB_2F_8$: C, 16.58; H, 2.79; N, 9.67. Found: C, 15.56; H, 2.89; N, 8.52.

2-Methyl-4-ethyl-1,2,4-thiadiazolium Diquat (6b).—Alkylation of 0.43 g (5 mmol) of 1,2,4-thiadiazole with triethyloxonium tetrafluoroborate (12 mmol) by method A for 1 hr at room temperature produced a two-phase system. Solution of the lower phase in acetone and addition of an equal volume of dichloromethane gave the monoquat, **4-ethyl-1,2,4-thiadiazolium tetrafluoroborate**: 0.7 g (70%); mp 68–70°; nmr (CF_3CO_2D, internal TMS) δ 1.80 (t, 3), 4.83 (q, 2), 9.26 (s, 1), 11.00 ppm (s, 1).

Reaction of 0.45 g (2.2 mmol) of the above monoquat with 0.43 g (2.9 mmol) of trimethyloxonium tetrafluoroborate by method B (30 min at 80–90°) gave a yellow semisolid. Recrystallization from 1:1 acetonitrile–DCE afforded **6b**: 0.3 g (45%); mp 143–145°; nmr (CF_3CO_2D, internal TMS) δ 1.88 (t, 3), 4.73 (s, 3), 5.05 (q, 2), 10.38 (s, 1), 11.33 ppm (s, 1).

(37) Prepared by an improved procedure: T. J. Curphey, *Org. Syn.*, **51**, 142 (1971).

Anal. Calcd for $C_5H_{10}N_2SB_2F_8$: C, 19.77; H, 3.32; N, 9.22. Found: C, 19.90; H, 3.40; N, 9.22.

3,4-Dimethyl-1,3,4-thiadiazolium Diquat (7a).—Alkylation of 0.17 g (2 mmol) of 1,3,4-thiadiazole by 0.77 g (5.2 mmol) of trimethyloxonium tetrafluoroborate according to method B (30 min at 85–90°) gave the highly insoluble **7a**, purified by trituration with trifluoroacetic acid: 0.3 g (52%); mp 149–150°; nmr (CF_3CO_2H–H_2SO_4, external TMS) δ 4.50 (s, 6), 10.45 ppm (s, 2). A completely satisfactory elemental analysis could not be obtained for this substance.

Anal. Calcd for $C_4H_8N_2SB_2F_8$: C, 16.58; H, 2.78; H, 9.66. Found: C, 15.15, 15.22; H, 2.72, 2.82; N, 9.04, 9.16.

3-Ethyl-4-methyl-1,3,4-thiadiazolium Diquat (7b).—Reaction of equimolar amounts of 1,3,4-thiadiazole and triethyloxonium tetrafluoroborate by method A (30 min at room temperature) gave **3-ethyl-1,3,4-thiadiazolium tetrafluoroborate**, which crystallized directly from the reaction mixture in 88% yield: mp 92–93°; nmr (CF_3CO_2H, internal TMS) δ 1.80 (t, 3), 4.92 (q, 2), 9.68 (s, 1), 10.40 ppm (s, 1).

Treatment of the above monoquat (0.4 g, 2 mmol) with trimethyloxonium tetrafluoroborate (0.38 g, 2.6 mmol) by method B (88–90° for 30 min) gave crude **7b**, purified by crystallization from 1:1 acetonitrile–DCE: 0.1 g (17%); mp 136–137°; nmr (3:1 CF_3CO_2D–D_2SO_4, external TMS) δ 1.80 (t, 3), 4.70 (s, 3), 4.99 (q, 2), 10.74 (s, 1), 10.84 ppm (s, 1).

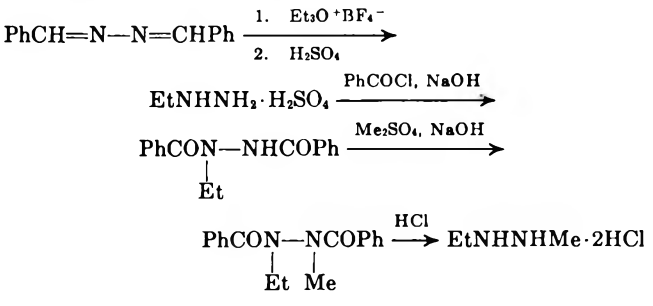
Anal. Calcd for $C_5H_{10}N_2SB_2F_8$: C, 19.73; H, 3.29; N, 9.29. Found: C, 19.72; H, 3.17; N, 9.06.

Catalytic Reduction of 1,4-Diethylpyrazine Diquat (1).—A flask containing 500 mg (0.16 mol) of **1**, 150 mg of 10% palladium on charcoal, and a Teflon-coated stirring bar was attached to a standard atmospheric hydrogenation apparatus and flushed with hydrogen. Reduction was initiated by injecting 10 ml of absolute ethanol through a serum-capped sidearm of the flask. Uptake of hydrogen amounted to 75% of theory over a 2-hr period. The reaction mixture was diluted with water and filtered, and the filtrate was evaporated. The crude product was dissolved in hot ethanol, the resulting suspension was centrifuged to remove a small amount of unidentified material, and the centrifugate was cooled to give 300 mg (59%) of 1,4-diethylpiperazine bishydrotetrafluoroborate, mp 166–168°. The ir and nmr spectra and mixture melting point of this material were identical with those of an authentic sample (*vide infra*).

1,4-Diethylpiperazine bishydrotetrafluoroborate.—Neutralization of 0.71 g of 1,4-diethylpiperazine[38] in 10 ml of absolute alcohol with concentrated fluoroboric acid, followed by evaporation *in vacuo* and recrystallization of the residue from alcohol, gave 1,4-diethylpiperazine bishydrotetrafluoroborate: 1.54 g (97%); mp 162–166°, raised to 166–168° by three recrystallizations from alcohol; nmr (D_2O, external TMS) δ 0.98 (t, 6), 2.98 (q, 4), 3.30 (s, 8), 4.32 ppm (s, 2); ir (KBr) 2500 (NH^+), 1050 cm^{-1} (BF_4^-).

Anal. Calcd for $C_8H_{20}N_2B_2F_8$: C, 30.22; H, 6.34; N, 8.81. Found: C, 30.40; H, 6.50; N, 8.70.

1-Methyl-2-ethylhydrazine Dihydrochloride.—This was synthesized by the four step sequence shown.



A. Ethyl Hydrazine Sulfate.—The procedure used was an adaptation of a synthesis of methylhydrazine sulfate.[39] To a solution of 38 g (0.2 mol) of triethyloxonium tetrafluoroborate in 70 ml of dry dichloromethane was added with stirring and exclusion of moisture 41.6 g (0.2 mol) of benzalazine in 40 ml of dry dichloromethane. After the solution was stirred for 3 hr, 21.6 ml of 9 *M* sulfuric acid was added, and the mixture was steam distilled to remove solvent and benzaldehyde. The nonvolatile residue was evaporated to dryness *in vacuo* and recrystallized from 100 ml of 80% alcohol to give ethyl hydrazine sulfate: 30 g (95%); mp 125–126° (lit.[40] mp 125–125.5°); nmr (CF_3CO_2H, internal TMS) δ 1.54 (t, 3), 3.75 ppm (q, 2).

B. 1-Ethyl-1,2-dibenzoylhydrazine.—Hatt's procedure for the preparation of dibenzoylhydrazine from benzoyl chloride and hydrazine sulfate[41] when applied to 8 g (0.05 mol) of ethylhydrazine sulfate gave 1-ethyl-1,2-dibenzoylhydrazine, recrystallized from glacial acetic acid: 13.3 g (98%); mp 95–97° (lit.[42] mp 133°); nmr ($CDCl_3$, internal TMS) δ 1.20 (t, 3), 3.78 (q, 2), 7.20–7.70 (m, 10), 8.11 ppm (s, 1).

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.45. Found: C, 71.42; H, 5.97; N, 10.29.

C. 1-Methyl-2-ethyl-1,2-dibenzoylhydrazine.—Application of Hatt's procedure for the methylation of dibenzoylhydrazine[41] using 14 g (0.052 mol) of 1-ethyl-1,2-dibenzoylhydrazine as starting material and one-half the recommended amount of methyl sulfate gave 1-methyl-2-ethyl-1,2-dibenzoylhydrazine, recrystallized from chloroform–ether: 8 g (54%); mp 74–75°. The nmr spectrum in $CDCl_3$ (internal TMS) was temperature dependent, presumably due to hindered rotation.[43] At 58° rotation was rapid enough to approach a simple averaged spectrum: δ 1.22 (t, 3), 3.20 (s, 3), 3.6 (b, 2), 7.3 ppm (s, 10).

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.14; H, 6.49; N, 9.90.

D. 1-Methyl-2-ethylhydrazine Dihydrochloride.—Hydrolysis of 1-methyl-2-ethyl-1,2-dibenzoylhydrazine (7 g, 0.025 mol) with hydrochloric acid was carried out in a manner identical with Hatt's procedure for the hydrolysis of dibenzoyldimethylhydrazine,[41] except that by-product benzoic acid was removed by extraction with benzene rather than by steam distillation. Crystallization from isopropyl alcohol–ether gave 1-methyl-2-ethylhydrazine dihydrochloride: 2.1 g (58%); mp 155–156°; nmr (D_2O, external TMS) δ 1.58 (t, 3), 3.14 (s, 3), 3.51 ppm (q, 2).

Anal. Calcd for $C_3H_{12}N_2Cl_2$: C, 24.50; H, 8.22; N, 19.05. Found: C, 24.78; H, 8.28; N, 19.25.

Amine Trifluoroacetamides.—The same general procedure was used for all amides. Trifluoroacetic anhydride (10.5 g, 0.05 mol) was added with ice cooling to a stirred mixture of amine hydrochloride or hydrazine dihydrochloride (0.01 mol), pyridine (4 g, 0.05 mol), and ether (5 ml). The mixture was allowed to warm up, stirred for 15 min at room temperature, then cooled again in an ice bath, and excess anhydride was destroyed by slow addition of water. The ether layer was washed successively with water, sodium bicarbonate solution, hydrochloric acid, and water. After drying over anhydrous sodium sulfate, the ether was removed by distillation, and the amide was purified by preparative glc on a 0.25 in. × 7 ft column of 20% Apiezon L on 60/80 mesh acid-washed and silanized Chromosorb W, operated at 70° and 80 ml/min helium carrier gas. Retention times and other pertinent data are summarized in Table II.

Hydrolytic Degradation of Diquats.—The same general procedure was employed in all three cases. A solution of 2 mmol of diquat in 10 ml of 6 *M* sulfuric acid was refluxed for 2 hr and then steam distilled to remove nonbasic volatile by-products. The acid residue was strongly basified with sodium hydroxide solution and again steam distilled. The distillate was acidified with 5 ml of 6 *M* hydrochloric acid and evaporated *in vacuo*. Residual water was removed by several evaporations with absolute alcohol, followed by drying for 1 hr *in vacuo*. The weight of the crude amine hydrochlorides was found at this stage to be 70–80% of the calculated amount in the three cases examined. The crude hydrochlorides were converted to an ether solution of the trifluoroacetamides by the procedure outlined above. The nature and amount of each amide present was determined by glc comparison with solutions of authentic amides at known concentration. Quantitation was by matching of peak heights and is probably not very accurate (±20%). The results obtained are given in Table III. To confirm the identification, the amides from the degradation were separated and purified by preparative glc and their ir and nmr spectra were compared with those of authentic samples.

(38) F. G. Menn and A. Senior, *J. Chem. Soc.*, 4476 (1954).

(39) H. H. Hatt, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 395.

(40) W. Seibert, *Chem. Ber.*, **80**, 494 (1947).

(41) H. H. Hatt, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 208.

(42) R. Stolle, *Ber.*, **34**, 3268 (1901).

(43) J. R. Fletcher and I. O. Sutherland, *Chem. Commun.*, 687 (1970), and preceding papers.

TABLE II

PROPERTIES OF AMINE TRIFLUOROACETAMIDES[a]

Amine	Registry no.	Mp (bp), °C	Retention time, min	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
$MeNH_2$	815-06-5	51–52[b]	3	28.35	3.17	11.02	28.09	3.29	10.78
$EtNH_2$	1682-66-2	14–15[c]	4	34.05	4.29	9.92	34.06	4.27	9.71
$(MeNH)_2$	34638-32-9	(180–181)	10	28.58	2.39	11.11	28.73	2.53	11.53
MeNHNHEt	34638-38-0	(205–206)	14	31.59	3.02	10.52	31.81	3.27	10.24

Amine	Nmr. δ (CCl_4, internal TMS) CH_3–C	CH_3–N	CH_2N	NH
$MeNH_2$		2.86 (d)		7.6 (b)
$EtNH_2$	1.23 (t)		3.4 (q)	8.0 (b)
$(MeNH)_2$		3.35 (s)[d,e]		
MeNHNHEt	1.20 (t)	3.3 (m)[d]	3.7 (m)[d]	

[a] Satisfactory analytical data (±0.4% for C, H, and N) were reported for all new compounds listed in the table. [b] Lit. mp 50–51°: E. R. Bissell and M. Finger, *J. Org. Chem.*, 24, 1256 (1959). [c] Lit.[16] bp 90° (11 mm). [d] At 68°. [e] Multiplicity strongly temperature dependent.[43]

TABLE III

HYDROLYTIC DEGRADATION OF DIQUATS

Diquat	Yield of amines,[a] % $MeNH_2$	$EtNH_2$	$(MeNH)_2$	MeNHNHEt
5b	<1	35	<1	24
5c	<1	35	31	<1
7b	<1	<1	<1	79

[a] Per cent of trifluoroacetamide derivative formed.

Epr Studies.—The cell used was constructed from a T/S 10/30 male joint. This was sealed at one end and constricted near the ground joint, and a 4-mm side arm was sealed below the constriction. A weighed sample of diquat contained in a short melting point capillary was placed in the cell, and the cell was attached to a vacuum line and evacuated to below 1-μ pressure. A well-degassed sample of solvent was then distilled onto the diquat and the cell was sealed off at the constriction. After shaking to dissolved the diquat, the epr spectrum was observed by inserting the cell side arm into the spectrometer cavity. Solutions in methyl, ethyl, isopropyl, and *tert*-butyl alcohols gave essentially identical spectra. With *tert*-butyl alcohol the initially rather weak spectrum increased in intensity upon standing. It was observed that the diquat appeared to be only slightly soluble in this alcohol, and the increasing intensity was attributed to a slow solution with reaction. For generation of radicals in trifluoroacetic acid the cell was modified by addition of a second side arm in which was placed a few small pieces of granulated zinc. After the usual degassing and sealing off, the diquat solution was *very briefly* contacted with the zinc to generate the radicals. Too long a contact with the zinc resulted in disappearance of the epr spectrum, indicating further reduction of the radicals to nonparamagnetic species.

Decomposition of 1 in Isopropyl Alcohol.—A suspension of 0.31 g (1 mmol) of diquat 1 in 2 ml of isopropyl alcohol was stirred under nitrogen. At intervals 0.1-ml aliquots were withdrawn, and the volatiles were removed by transfer on a vacuum line. The resulting distillate was examined by glc on a Carbowax 20M column. No acetone was found in aliquots taken after 30 min, after several hours, and after stirring overnight. When 7 μl of acetone was added to the now very dark reaction mixture and an aliquot was taken 1 hr later, a large acetone peak was present in the glc. Evaporation of solvent from the remainder of the reaction mixture gave a dark oil which could not be induced to crystallize.

Registry No.—**1,** 3552-55-4; **2a,** 3552-56-5; **2b,** 3552-57-6; **2c,** 3552-58-7; **3a,** 3817-04-7; **3b,** 3552-59-8; **4a,** 34630-77-8; **4b,** 34630-78-9; **5a,** 34630-79-0; **5b,** 34630-80-3; **5c,** 34630-81-4; **6a,** 34630-82-5; **6b,** 34647-03-5; **7a,** 34630-83-6; **7b,** 34630-84-7; 1-ethylpyridazinium tetrafluoroborate, 34630-85-8; 1-methyl-4-ethyl-1,2,4-triazolium tetrafluoroborate, 34630-86-9; 4-ethyl-1,2,4-thiadiazolium tetrafluoroborate, 34630-87-0; 3-ethyl-1,3,4-thiadiazolium tetrafluoroborate, 15681-47-7; 1,4-diethylpiperazine bishydrotetrafluoroborate, 34630-89-2; ethylhydrazine sulfate, 34638-34-1; 1-ethyl-1,2-dibenzoylhydrazine, 30719-96-1; 1-methyl-2-ethyl-1,2-dibenzoylhydrazine, 30719-97-2; 1-methyl-2-ethylhydrazine 2HCl, 18247-20-6.

Acknowledgment.—Support from the National Science Foundation Grant No. GP-8510 for the 100-MHz nmr spectrometer is gratefully acknowledged.

Reactions of *tert*-Butyl Peresters. XI. Reactions of Alkyl *tert*-Butylperoxy Alkylphosphonates, Dialkyl *tert*-Butylperoxy Phosphates, and Other Phosphorus Esters with Benzene and Aluminum Chloride, and Reactions of Dialkyl *tert*-Butylperoxy Phosphates with Phenylmagnesium Bromide[1]

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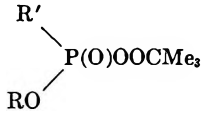
Reactions of alkyl *tert*-butylperoxy alkylphosphonates (1), dialkyl *tert*-butylperoxy phosphates (2), and other phosphorus compounds of general structure **3** [R = alkyl; R′ = alkyl, alkoxy; X = OR, OH, H, Cl, OP(O)R′(OR), $OCMe_3$] with benzene in the presence of aluminum chloride proceed rapidly at 5° to produce primarily the corresponding monoalkyl benzene derived from cleavage of the P···O···R linkage of the phosphorus compound. In the cases of **1** and **2**, *tert*-butylbenzene and phenol are also found, derived from cleavage of the peroxide linkage. Reactions of dialkyl *tert*-butylperoxy phosphates (2) with phenylmagnesium bromide produce high yields of *tert*-butyl phenyl ether and moderate to high yields of the corresponding dialkylphosphoric acid **8**.

The ability of organophosphorus esters to alkylate alcohols and amines is well documented and has been recognized for many years. These reactions usually proceed at elevated temperatures and generally do not require catalysts.[2] Nucleophilic reactions involving organophosphorus compounds both *in vivo* and *in vitro* have been the subject of an enormous amount of research.[3] In contrast, electrophilic reactions involving organophosphorus esters are relatively unexplored.

We have been systematically investigating the chemistry of peroxy phosphates **1** and **2** (R, R′ = alkyl) as model systems for hypothetical intermediates *in vivo*. In view of the apparent implication of alkylation re-



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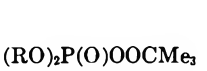
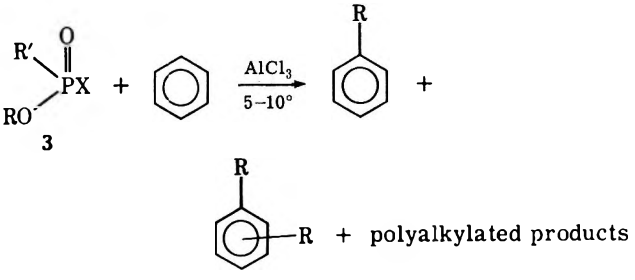


2

actions in carcinogenesis and cancer chemotherapy,[4] and of dealkylation reactions in the aging of phosphorylated enzymes,[5] it was of interest to examine the alkylation reactions of peresters **1** and **2** under both electrophilic and nucleophilic conditions. We have reported on our investigation of the reaction of peresters **2** with amines[6] and triphenylphosphine.[7] Now we wish to report on the reactions of **1** and **2** and other phosphorus compounds (**3**) containing P···O···R linkages with benzene in the presence of aluminum chloride and on the reactions of **2** with phenylmagnesium bromide.

Although the Friedel–Crafts type reactions of esters of carboxylic acids have been widely studied, relatively few investigations of the analogous reactions of esters of inorganic acids have been reported.[8] The reactions of organophosphorus esters have, to our knowledge, been discussed only in three short papers. Thus, the reactions of trialkyl phosphates (**3**, R = C_2H_5, *i*-C_3H_7, *n*-C_4H_9; X, R′ = OR) with benzene in the presence of either aluminum chloride[9,10] or boron trifluoride[11] give the corresponding aralkyls. None of these studies dealt with the details and scope of these reactions.

Our studies show that the reactions of phosphorus compounds of general structure **3** (R = alkyl; R′ = alkyl, alkoxy; X = H, OH, OR, Cl, OP(O)(OR)R′, $OCMe_3$) containing P···O···R linkages readily proceed at 5–10° with benzene in the presence of aluminum chloride to give alkylated benzenes. The results



shown in Table I indicate that the variations in the structure of the phosphorus ester have no decisive effect on the nature and yield of products.[12] In all cases, the O–C bond was cleaved to give the attacking

(1) (a) This investigation was supported by grants from the Public Health Service, U. S. Department of Health, Education, and Welfare (GM 16741) and from the Graduate School of the University of Wisconsin—Milwaukee. (b) For the previous paper in this series see ref 7.

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(11) J. F. McKenna and F. J. Sowa, *J. Amer. Chem. Soc.*, **59**, 1204 (1937).

(12) It should be noted that the use of phosphorus esters as alkylating agents for aromatic compounds on laboratory scale has a potential synthetic value since they are industrially available, nontoxic liquids as opposed to most low molecular weight alkylating agents, which are gases.

TABLE I

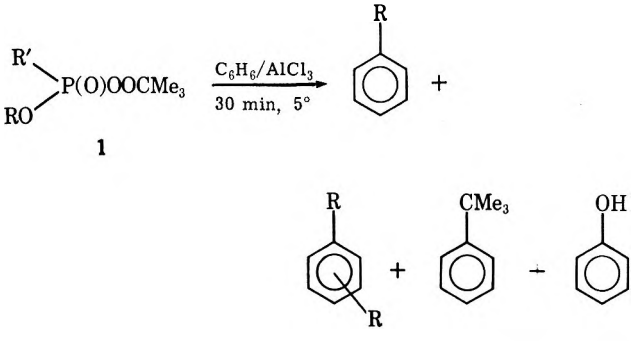
PRODUCTS OF THE REACTIONS OF ORGANOPHOSPHORUS ESTERS, RO(R')P(O)X, WITH BENZENE IN THE PRESENCE OF ALUMINUM CHLORIDE

Registry no.	R	R'	X	C_6H_5R, %	$C_6H_4R_2$, %	Registry no.	R	R'	X	C_6H_5R, %	$C_6H_4R_2$, %
78-40-0	C_2H_5	C_2H_5O	C_2H_5O	17	33	34637-92-8	CH_3	C_2H_5	OH	36	4
513-02-0	i-C_3H_7	i-C_3H_7O	i-C_3H_7O	42	13	1832-53-7	C_2H_5	CH_3	OH	92	1
126-73-8	n-C_4H_9	n-C_4H_9O	n-C_4H_9O	34[a]		1832-54-8	i-C_3H_7	CH_3	OH	95	<1
6163-75-3	CH_3	C_2H_5	CH_3O	33	7	1832-55-9	n-C_4H_9	CH_3	OH	90[j]	<1
683-08-9	C_2H_5	CH_3	C_2H_5O	27	24	32288-17-8	C_2H_5	CH_3	OP(O)	69	1
	C_2H_5	CH_3	C_2H_5O[b]	12	8				CH_3(OEt)		
	C_2H_5	CH_3	C_2H_5O[c]	1		34637-96-2	CH_3	C_2H_5	OP(O)	64	<1
	C_2H_5	CH_3	C_2H_5O[b,d]	32	18				(OMe)Et		
1445-75-6	i-C_3H_7	CH_3	i-C_3H_7O	43	7	34637-97-3	C_2H_5	CH_3	$OCMe_3$	76[k]	1
1067-69-2	i-C_3H_7	C_2H_5	i-C_3H_7O	2	12	34637-98-4	i-C_3H_7	C_2H_5	$OCMe_3$	70[l]	
2404-73-1	n-C_4H_9	CH_3	n-C_4H_9O	59[e]	8	813-77-4	CH_3	CH_3O	Cl	20	9
2404-58-2	n-C_4H_9	C_2H_5	n-C_4H_9O	36[f]	4	814-49-3	C_2H_5	C_2H_5O	Cl	31	47
762-04-9	C_2H_5	C_2H_5O	H	30	12	10419-79-1	i-C_3H_7	i-C_3H_7O	Cl	43	2
1809-20-7	i-C_3H_7	i-C_3H_7O	H	16[g]	6	5284-09-3	C_2H_5	CH_3	Cl	40[m]	
	i-C_3H_7	i-C_3H_7O	H	30[h]	3		C_2H_5	CH_3	Cl	32[n]	28
1809-19-4	n-C_4H_9	n-C_4H_9O	H	7[i]		1445-76-7	i-C_3H_7	CH_3	Cl	64[c,o]	
17176-77-1	$C_6H_5CH_2$	$C_6H_5CH_2O$	H	60							

[a] n-Bu 8%, *sec*-Bu 26%. [b] Reaction time 2 hr at 10°. [c] Method 2. [d] Reaction time 4 hr at room temperature. [e] n-Bu 8%, *sec*-Bu 51%. [f] Bu 4%, *sec*-Bu 32%. [g] Reaction time 1 hr at room temperature. [h] Reaction time 24 hr at room temperature. [i] n-Bu 15%, *sec*-Bu 52%. [j] n-Bu 19%, *sec*-Bu 71%. [k] And *tert*-butyl benzene 37%. [l] And *tert*-butylbenzene 72%. [m] Reaction time 20 hr at room temperature. [n] Reaction time 1 hr at 5° and then 24 hr at room temperature. [o] Reaction time 36 hr at room temperature.

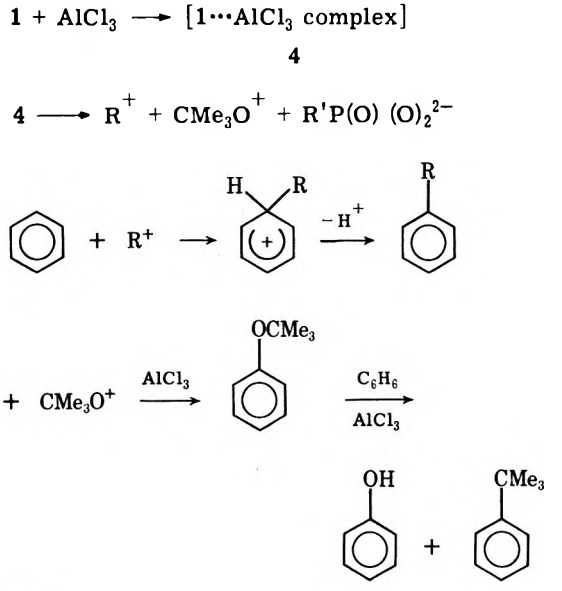
carbonium ion, R^+, while no products derived from P–C cleavage were detected. The reaction does not proceed when R is aromatic. Thus, the reactions of triphenyl phosphate (**3**, R = C_6H_5; X, R' = C_6H_5O) form no products derived from P···O···C_6H_5 cleavage.[13]

The reactions of peresters of alkylphosphonic acids (**1**, R = Me, Et, *i*-Pr, *n*-Bu; R' = Me, Et) in the presence of aluminum chloride were investigated under a variety of conditions. With high dilution, *i.e.*, large benzene to peroxy alkylphosphonate ratio, *e.g.*, 135:1, lowered temperature (5°), and short stirring time (15–30 min), the following products, resulting from cleavage of both the O–C and the O–O–C linkages, are isolated.



This reaction is rather sensitive to experimental conditions. With the ratio of $1:AlCl_3:C_6H_6$ = 0.01:0.034:1.35, low temperature (5°), and short duration (15 min), the amount of *tert*-butylbenzene is 8–35%, phenol is 12–66%, and alkylation is 40–85% with monosubstitution predominating. If the ratio is changed to 0.05:0.1:0.8, or the reaction time is increased to 20 hr and the temperature to 23–26°, the *tert*-butylbenzene and phenol are no longer detected, while the amount of dialkylation increases (Table II). It has been shown in our laboratory that the use of methylene chloride–nitromethane solutions of aluminum chloride and benzene results in nonisomerizing conditions for the reactions of phosphorus esters.[14] If the "milder" complex of $AlCl_3$–CH_3NO_2 is used for the reaction of **1** with benzene, the amount of *tert*-butylbenzene isolated is much greater (50%) while the amount of alkylated product derived from the RO moiety is low especially when the incipient carbonium ion is CH_3^+ or $C_2H_5^+$ (Table II).

The formation of *tert*-butylbenzene and phenol might be explained by a mechanism in analogy to the proposed mechanism for the reaction of *tert*-butyl hydroperoxide with toluene.[15] Since the O···O linkage is the weakest bond in the peroxide molecule, the initial heterolytic cleavage probably occurs at this bond, aided by the polarization enhanced by the electrophilic Lewis acid. Coordination of the aluminum chloride probably involves all oxygens of the



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(14) M. W. Shende, M.S. Thesis, University of Wisconsin—Milwaukee, 1971.

(15) S. Hashimoto and W. Koike, *Bull. Chem. Soc. Jap.*, **43**, 293 (1970).

TABLE II

PRODUCTS FROM THE REACTIONS OF (RO)R'P(O)OOCMe$_3$ WITH BENZENE IN THE PRESENCE OF ALUMINUM CHLORIDE

Registry no.	R	R'	Experimental method[a]	Product yield, % RC$_6$H$_5$ R =	RC$_6$H$_5$	Me$_3$CC$_6$H$_5$	HOC$_6$H$_5$	Alkyl group accounted as aralkyls, %
6795-02-4	Me	Et	A	Me	40	6	7	40
	Me	Et	C	Me	0.5	35	13	0.5
31238-29-6	Et	Me	A	Et	69	15	9	69
	Et	Me	C	Et	0.5	44	15	0.5
	Et	Me	B	Et	95	0	0	95
31238-30-9	*i*-Pr	Me	A	*i*-Pr	62	11	8	62
	i-Pr	Me	C	*i*-Pr	53	33	17	53
	i-Pr	Me	C[b]	*i*-Pr	67	40	10	67
31238-31-0	*i*-Pr	Et	A	*i*-Pr	62	12	9	62
	i-Pr	Et	C	*i*-Pr	66	25	20	66
31238-32-1	*n*-Bu	Me	A	*n*-Bu	46.5	2	2	83
				sec-Bu	35			
	n-Bu	Me	C	*n*-Bu	17	2	2	20
				sec-Bu	3			
31246-33-0	*n*-Bu	Et	A	*n*-Bu	50	3	2	85
				sec-Bu	35			
	n-Bu	Et	C	*n*-Bu	20	3	2	30
				sec-Bu	10			

[a] See Experimental Section for details. [b] Reaction time 24 hr at room temperature.

TABLE III

PRODUCTS OF THE REACTIONS OF BENZENE SOLUTIONS OF DIALKYL *tert*-BUTYLPEROXY PHOSPHATES, (RO)$_2$P(O)OOCMe$_3$, WITH BENZENE IN THE PRESENCE OF ALUMINUM CHLORIDE[a]

Registry no.	(RO)$_2$P(=O)-OOCMe$_3$ R =	AlCl$_3$, mol	Reaction time after addition, hr	Reaction of R group, %		Yield, % C$_6$H$_5$R	C$_6$H$_4$R$_2$	C$_6$H$_5$CMe$_3$	C$_6$H$_5$OH
10160-45-9	Et	0.038	0.5	33		33	<1	16	6
	Et	0.034	20	90		90	<1	0	14
18963-66-1	*n*-Pr	0.038	0.5	71.5	*n*-C$_3$H$_7$	15	16.5	20	12
					i-C$_3$H$_7$	40			
10160-46-0	*i*-Pr	0.03	20	74		24	50	0	12
	i-Pr	0.034	0.5	64		52	12	15	<1
10160-47-1	*n*-Bu	0.038	0.5	60	*n*-C$_4$H$_9$	0	<1	21	23
					sec-C$_4$H$_9$	60			

[a] Stirred at 5° for 15 min after addition; products analyzed by glc.

perester to some extent and aids in the formation of the alkyl (R^+) and alkoxy (CMe_3O^+) species which subsequently react with the aromatic nucleus.

Under similar conditions the reaction of *tert*-butyl hydroperoxide with benzene produces a mixture of *tert*-butylbenzene and phenol in 15–20% yield, whereas in the presence of aluminum chloride–nitromethane this reaction results only in a 10% yield of a 1:1 mixture of the same products even after 20 hr of reaction.

The analogous reaction of diisopropyl *tert*-butylperoxy phosphate (2, R = *i*-C_3H_7) with benzene and aluminum chloride at 5° produces mainly cumene, diisopropylbenzene, phenol, and, depending on the reaction conditions, *tert*-butylbenzene. The *tert*-butylbenzene is found only if the reaction is worked up soon after the addition of the perester is completed. If the reaction mixture is kept at ambient temperature for 24 hr or if the perester is added neat at 5–15°, little or no *tert*-butylbenzene is isolated. These results are consistent with the rearrangements and dealkylation reactions which have been reported for *tert*-butyl phenyl ether and *tert*-butylbenzene under similar conditions.[16] The products of the reactions of peresters 2 with benzene and aluminum chloride are shown in Table III. Similarly, solutions of aluminum chloride and benzene in nitromethane–methylene chloride react with methylene chloride solutions of peresters 2 to produce mainly the corresponding monoalkylbenzene and *tert*-butylbenzene and low yields of phenol and dialkylbenzene. The results of the glc analyses of these experiments are presented in Table IV. The dialkylbenzenes were detected in such small amounts that their yields are insignificant.

TABLE IV

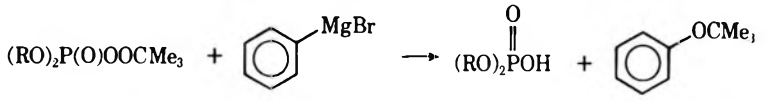
PRODUCTS FROM THE REACTIONS OF DIALKYL *tert*-BUTYLPEROXY PHOSPHATES, (RO)$_2$P(O)OOCMe$_3$, WITH BENZENE AND ALUMINUM CHLORIDE IN NITROMETHANE–METHYLENE CHLORIDE SOLUTION

(RO)$_2$P(=O)OOCMe$_3$ R =	Reaction time after addition, hr	Reaction of R group, %		Yield, % C$_6$H$_5$R	C$_6$H$_5$CMe$_3$	C$_6$H$_5$OH
Et	4	2		2	40	<1
n-Pr	4	20	*n*-C$_3$H$_7$	13	55	5
			i-C$_3$H$_7$	7		
i-Pr	20	90		90	56	4
i-Pr	3	21		21	16	2
n-Bu	4	38	*n*-C$_4$H$_9$	38	40	2
			sec-C$_4$H$_9$	0		

(16) S. Natelson, *J. Amer. Chem. Soc.*, **56**, 1583 (1934), and references cited therein.

TABLE V

REACTION OF DIALKYL *tert*-BUTYLPEROXY PHOSPHATES WITH PHENYLMAGNESIUM BROMIDE



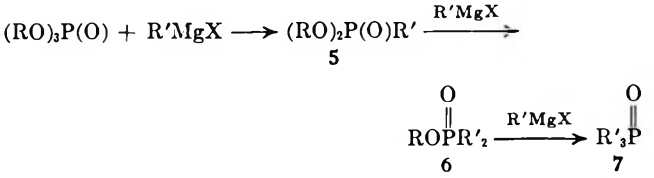
Perester 2 R =	Amount of perester 2, mol	C_6H_5Br, mol	Method	Addition time, hr	Addition temp, °C	Additional stirring, hr	Additional stirring temp, °C	Yield of $C_6H_5OCMe_3$, %	Yield o $(RO)_2P$ (=O)OI %
i-C_3H_7	0.03	0.05	A	0.58	10–15	0.1	10	60	*a*
C_2H_5	0.03	0.05	A	1.33	5–10	4	*b*	78	*a*
n-C_4H_9	0.03	0.05	A	0.5	4–15	19	*b*	74	*a*
C_2H_5	0.03	0.063	B		5–15	1	0–5	82	30
n-C_3H_7	0.023	0.063	B		5–15	0.25	5		
						0.75	*b*	86	58
i-C_3H_7	0.03	0.063	B		5–15	0.25	5		
						0.50	*b*	88	71
n-C_4H_9	0.03	0.063	B		5–15	0.25	5		
						1.0	*b*	95	88

[a] Identified spectroscopically. [b] Room temperature.

The reactions of *tert*-butyl perbenzoate with Grignard reagents produce high yields of the *tert*-butyl ether derived from the Grignard reagent,[17] whereas the

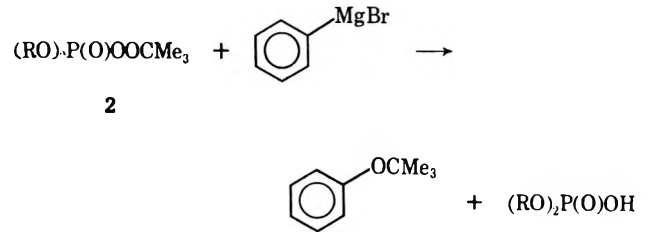
$$C_6H_5C(O)OOCMe_3 + ArMgX \longrightarrow C_6H_5C(O)OH + ArOCMe_3$$

reaction of phosphate esters with Grignard reagents has been found to involve nucleophilic displacement of alkoxy or aryloxy groups in a stepwise sequence to yield the corresponding phosphonate (**5**), phosphinate (**6**), and phosphine oxide (**7**).[18]



R, R′ = alkyl, aryl

We have now found that the reaction of phosphorus peresters **2** (R = alkyl) with the phenyl Grignard reagent follow the pathway of the carbon peresters and not that of phosphate esters to give high yields of *tert*-butyl phenyl ether and moderate to high yields of the corresponding dialkylphosphoric acid **8** (Table V). In addition, low yields of biphenyl and phenol are isolated. These products are formed as a result of using regular grade magnesium without further purification.



Experimental Section

Trialkyl phosphates were commercial samples and were distilled before use. Dialkyl hydrogen phosphites and dialkyl phosphorochloridates were prepared by the method of Fiszer Michalski.[19] Dialkyl *tert*-butyl-[7] and dialkyl *tert*-butylper phosphates[20] were prepared as described in our earlier pap The dialkyl alkylphosphonates were prepared *via* the Arbu reaction.[21] The phosphonochloridates in turn were rea obtained by chlorination with PCl_5 of the Arbuzov produc The alkylphosphonic acid monoesters were prepared by alka hydrolysis[23] of the same Arbuzov products. The dialkyl dial pyrophosphonates were prepared by reaction of the correspon chlorides in the presence of base such as pyridine and wat while the *tert*-butyl alkyl esters of alkylphosphonic acid synthesized from the corresponding chlorides and potassium butoxide.[25] Alkyl *tert*-butylperoxy alkylphosphonates prepared by way of the parent chlorides and were then pur with lead tetraacetate to give analytically pure samples follo a distillation in small lots.[26]

The benzene used as substrate and solvent was distilled and stored over sodium. All other materials were best mercial grade available used without further purification. analyses were performed on a Varian Aerograph Model dual column instrument equipped with WX detectors a linear temperature programmer. The areas of the peak tained were determined either by triangulation or with a pla eter. All boiling points and melting points are uncorrected.

Analytical Procedures.—An Aerograph 1700 dual-columi chromatograph was used. The following overall condi were maintained: block temperature, 225°; injector ten ature, 215°; bridge current, 150 mA; sample size, 2 μl with the appropriate attenuations. Column 1 was 6 ft × 0.25 in., 20% Carbowax 20M on Chromosorb W, 80–180°, 40–50 ml of He/min. Column 2 was 5 ft × 0.25 in., 3% SE-30 on Varapack, 80–200°, 40–50 ml of He/min. All identification of products was by comparison of retention times and "spiking" with authentic samples. Infrared analysis for verification of the presence of various functional groups was performed on a Perkin-Elmer Infracord spectrophotometer, Model 137.

Reactions of Alkylphosphonates (3, X = OR, OH, OP(O)(OR)R′, Cl, $OCMe_3$). General Procedure 1 (Table I).—To a suspension of 0.09 mol of aluminum chloride in 90 ml (1.01 mol) of benzene was added dropwise a solution of 0.03 mol of phosphonate in 30 ml (0.34 mol) of benzene. After the addition, the mixture was stirred for 20 hr at room temperature and was then hydrolyzed by pouring it onto 50 ml of ice-cold 10% HCl.

(17) S.-O. Lawesson and N. C. Yang, *J. Amer. Chem. Soc.*, **81**, 4230 (1959); C. Frisell and S.-O. Lawesson, *Org. Syn.*, **41**, 91 (1961).

(18) K. D. Berlin and M. E. Peterson, *J. Org. Chem.*, **32**, 125 (1967), and references cited therein.

(19) B. Fiszer and J. Michalski, *Rocz. Chem.*, **26**, 688 (1952).

(20) G. Sosnovsky and E. H. Zaret, *J. Org. Chem.*, **34**, 968 (1969).

(21) (a) A. E. Arbuzov and N. P. Kushkova, *J. Gen. Chem. USSR*, **6**, 283 (1936); (b) G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **66**, 1511 (1944); (c) A. H. Ford-Moore and J. H. Williams, *J. Chem. Soc.*, 1465 (1947).

(22) A. I. Razumov, E. A. Markovich, and O. A. Mukhacheva, *Khim. Primen. Fosfororg. Soedin., Tr. Konf., 2nd*, 194 (1955); *Zh. Obshch. Khim.*, **27**, 2389 (1957).

(23) R. Rabinowitz, *J. Amer. Chem. Soc.*, **82**, 4566 (1960).

(24) D. G. Coe, B. J. Perry, and R. K. Brown, *J. Chem. Soc.*, 3604 (1957).

(25) Prepared in analogy with the method described in ref 7.

(26) G. Sosnovsky and M. Konieczny, *Synthesis*, 144 (1971).

The organic layer was separated, and the aqueous layer was extracted several times with ether. The combined organic layers were washed with 10% sodium bicarbonate solution and then water, dried ($MgSO_4$), and concentrated by distillation of the solvents at 1 atm pressure under nitrogen. The products were analyzed by gas chromatography.

General Procedure 2.—To a cooled (10°) solution of 120 ml (1.35 mol) of benzene and 80 ml (1.26 mol) of methylene chloride was added a cooled (10°) solution of 0.034 mol of aluminum chloride in 12 ml of nitromethane. To the well-stirred mixture was then added at 5° a solution of 0.01 mol of phosphonate **3** in 12 ml (0.19 mol) of methylene chloride. After stirring at ambient temperature for 20 hr, the reaction mixture was hydrolyzed by the dropwise addition of ice water at 5–10°. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were then washed with 10% sodium bicarbonate solution and then water, dried ($MgSO_4$), and concentrated by distillation of the solvents at 1-atm pressure under nitrogen. The products were identified by gas chromatography.

Reactions of Alkyl *tert*-Butylperoxy Alkylphosphonates (1). General Procedures (Table II). A. In Benzene.—To a well-stirred suspension of 0.034 mol of aluminum chloride in 90 ml (1.01 mol) of benzene was added at 5° a solution of 0.01 mol of alkyl *tert*-butylperoxy alkylphosphonate in 30 ml (0.34 mol) of benzene. The reaction mixture was then stirred at 5° for 15 min, and was then hydrolyzed by pouring it onto 25 ml of ice-cold 10% HCl. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with 10% sodium bicarbonate solution and then water, dried ($MgSO_4$), and concentrated by distillation of the solvents at 1 atm pressure under nitrogen. The products were then identified by gas chromatography.

B. In Benzene.—To a well-stirred suspension of 0.10 mol of aluminum chloride in 70 ml (0.79 mol) of benzene was added, as rapidly as possible at 5–10°, 0.05 mol of alkyl *tert*-butylperoxy alkylphosphonate. The reaction mixture was then stirred at 5° for 1 hr and at ambient temperature for 36 hr, and was then hydrolyzed by the dropwise addition of 75 ml of water at 5–10°. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with 10% sodium bicarbonate solution and then water, dried ($MgSO_4$), and concentrated by distillation of the solvents at 1 atm pressure under nitrogen. The products were then identified by gas chromatography.

C. In Methylene Chloride.—To a cooled (10°) solution of 120 ml (1.35 mol) of benzene and 80 ml (1.26 mol) of methylene chloride was added a cooled (10°) solution of 0.034 mol of aluminum chloride in 12 ml of nitromethane. To this mixture then was added at 5° a solution of 0.01 mol of alkyl *tert*-butylperoxy alkylphosphonate in 12 ml (0.19 mol) of dichloromethane. The reaction was then stirred at ambient temperature for 4 hr, and was hydrolyzed by the dropwise addition of 50 ml of ice water. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with 10% sodium bicarbonate solution and then water, dried ($MgSO_4$), and concentrated by distillation of the solvents at 1 atm pressure under nitrogen. The products were then identified by gas chromatography.

Reactions of Dialkyl Phosphate Esters (3, R′ = OR; X = OR, Cl, H). General Procedure 3 (Table I).—The ester (0.2 mol) was added at 8–10° over 1 hr to a well-stirred suspension of 93.6 g (0.7 mol) of aluminum chloride in 355 ml (4.0 mol) of benzene. The mixture was stirred for 1 hr and was then poured onto crushed ice. The organic layer was separated, washed with 5% sodium bicarbonate solution (2 × 50 ml) and then 50 ml of water, dried ($CaCl_2$), and fractionally distilled, yielding the alkyl benzenes, whose identity and purity were confirmed by glc.

Reactions of *tert*-Butyl Hydroperoxide. A. In Benzene.—A solution of 0.15 mol of *tert*-butyl hydroperoxide (dried over $MgSO_4$) in 90 ml (1.01 mol) of benzene was added at 5–8° to a suspension of 0.30 mol of aluminum chloride in 270 ml (3.04 mol) of benzene. The reaction was stirred at 5° for 2 hr, and worked up according to General Procedure 1. The organic extract was then concentrated to give 7.04 g (35%) of *tert*-butylbenzene which was identified by ir and gas chromatography. Acidification of the base extract followed by extraction with ether afforded, after washing with water and drying ($MgSO_4$), 4.70 g (33%) of phenol, as identified by ir and gas chromatography.

B. In Methylene Chloride.—To a cooled (15°) solution of 120 ml (1.35 mol) of benzene and 80 ml (1.26 mol) of methylene chloride was added a cooled (10°) solution of 0.35 mol of aluminum chloride in 15 ml of nitromethane. To this well-stirred mixture at 5° was then added a solution of 0.015 mol of *tert*-butyl hydroperoxide (dried over $MgSO_4$) in 12 ml of methylene chloride. The reaction was then stirred at ambient temperature for 20 hr, since there was no visible reaction after 4 hr, and was worked up according to General Procedure 2.

Reactions of Benzene Solutions of Dialkyl *tert*-Butylperoxy Phosphates 2 with Benzene in the Presence of Aluminum Chloride. General Procedure 4 (Table III).—A solution of dialkyl *tert*-butylperoxy phosphate (0.01 mol) in 30 ml (0.34 mol) of benzene was added at 5° over 45 min to a well-stirred suspension of 5.00 g (0.038 mol) of aluminum chloride in 90 ml (1.0 mol) of benzene. After the addition was completed, the cooling bath was removed and the mixture was stirred at ambient temperature for the specified time. The reaction mixture was hydrolyzed by pouring it into 120 ml of 10% ice cold hydrochloric acid solution. The organic layer was separated and the aqueous solution was extracted with ether. The combined organic layers were then washed with 10% sodium bicarbonate solution and then water, dried ($MgSO_4$), and concentrated by removal of the solvents by distillation at 1 atm pressure under nitrogen. The residual oils were analyzed by glc.

Reactions of Methylene Chloride Solutions of Dialkyl *tert*-Butylperoxy Phosphates 2 with Benzene and Aluminum Chloride in Nitromethane–Methylene Chloride Solution. General Procedure 5 (Table IV).—A precooled solution of 4.58 g (0.034 mol) of aluminum chloride in 12 ml (0.22 mol) of nitromethane was added to a cold (15°) solution of 120 ml (1.35 mol) of benzene and 80 ml (1.26 mol) of methylene chloride. To the resulting solution was added at 2–5° a solution of 0.01 mol of dialkyl *tert*-butylperoxy phosphate in 12 ml (0.19 mol) of methylene chloride. After the addition was completed, the ice water cooling bath was removed and the reaction mixture was stirred at ambient temperature for the specified time. Ice water was added dropwise over approximately 15 min and the organic layer was separated. The aqueous solution was extracted with ether and the combined organic layers were washed with 10% sodium bicarbonate solution and then water, dried ($MgSO_4$), and concentrated by removing the solvents by distillation at 1 atm pressure under nitrogen. The residual oils were analyzed by glc.

Reactions of Dialkyl *tert*-Butylperoxy Phosphates 2 with Phenylmagnesium Bromide. General Procedure 6. A. Preparative Method.—Bromobenzene (7.9 g, 0.05 mol) was added dropwise into a well-stirred mixture of 1.3 g (0.053 g-atom) of magnesium and 20 ml of absolute ether at such a rate as to maintain gentle reflux. After the addition was completed, the mixture was refluxed for 1 hr and was then cooled to 5°. Dialkyl *tert*-butylperoxy phosphate (0.03 mol) was added as specified in Table V. The mixture was then stirred for the prescribed period and hydrolyzed by the addition, with cooling, of 9 ml of saturated ammonium chloride solution. The liquid phase was decanted from the inorganic salt and was concentrated by distillation of the ether. The residual oil was then distilled to yield *tert*-butyl phenyl ether, bp 68–70° (10 mm) [lit.[17] bp 57–59° (7 mm)].

Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.60; H, 9.33.

B. Analytical Method. Determination of the Volatile Products by Glc and Isolation of Dialkyl Phosphates.—A solution of 9.88 g (0.063 mol) of bromobenzene in 40 ml of absolute ether was added with stirring to 1.63 g (0.066 g-atom) of magnesium at such a rate as to maintain gentle reflux. The mixture was refluxed for 1 hr after the addition was completed and was cooled to 5°. Anhydrous ether (40 ml) was added in one portion and then a solution of 0.03 mol of dialkyl *tert*-butylperoxy phosphate in 40 ml of anhydrous ether was added dropwise at 5–15°. After the addition was completed, the mixture was stirred with ice water cooling for 15 min and was then stirred at room temperature as specified in Table V. The mixture was hydrolyzed by adding 50 ml of water dropwise at 20°. The organic layer was separated. The aqueous layer was acidified with 10% hydrochloric acid solution and was extracted with ether. The combined ether solutions were washed several times with 10% sodium hydroxide solution and then distilled water, dried ($MgSO_4$), and concentrated on a rotary evaporator to yield an oil which was analyzed by glc on column 2.

The sodium hydroxide extracts were acidified with 10% hydrochloric acid solution and were then evaporated to dryness

in vacuo. The residual solids were extracted with ether several times and the combined ether extracts were dried ($MgSO_4$) and concentrated, yielding dialkyl phosphates (8) which were identified as their dicyclohexyl amine salts (Table VI).

Table VI

Registry no.	$(RO)_2P(O)OH$ R =	Dicyclohexyl Amine Salt Mp, °C (solvent)	Mmp,[a] °C
34608-90-7	Et	132–134 (ligroin)	133.5–134.5
14530-43-9	*n*-Pr	131–133 (acetone)	133–134
13941-64-5	*i*-Pr	171–173 (acetone)	172–173
34638-10-3	*n*-Bu	104–105 (acetone)	106–107

[a] Preparation of the authentic samples was reported in A. F. Gasiecki, M. S. Thesis, University of Wisconsin—Milwaukee, 1970.

Registry No.—Benzene, 71-43-2; $AlCl_3$, 7446-70-0; phenylmagnesium bromide, 100-58-3.

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Steric and Electronic Effects on the Stereochemistry of the Alkaline Hydrolysis of Acyclic Dialkoxyphosphonium Salts. Pseudorotation of Intermediates in Phosphorus Ester Reactions

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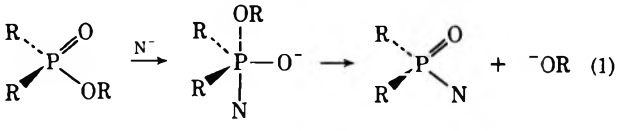
The stereochemistry of the alkaline hydrolysis of three acyclic dialkoxyphosphonium salts, (*R*)- and (*S*)-menthoxymethoxymethylphenylphosphonium hexachloroantimonate (2) and ethoxymethoxymethylphenylphosphonium hexachloroantimonate (3), was investigated and compared to the previous results obtained for the alkaline hydrolysis of (*R*)- and (*S*)-ethoxymenthoxymethylphenylphosphonium hexachloroantimonate (1). The extent to which the intermediate phosphorane containing one apical alkoxy group and one equatorial alkoxy group can undergo pseudorotation prior to direct loss of the apical alkoxide increases by a factor of 10 and 70 as the apical alkoxy group is varied from methoxy to ethoxy or menthoxy, respectively, but decreases by a factor of 0.6 and 0.3, respectively, as the same variation is made in the equatorial alkoxy group. Thus, depending only on the nature of the alkoxy ligands, a reaction can proceed either with predominant (>90%) direct loss of an alkoxide or predominantly by a pathway involving pseudorotation. In contrast to previous explanations, the "bulky" menthoxy group exerts no observable steric driving force to occupy the less hindered equatorial position of a phosphorane. The extension of these results to the relative stability of intermediates in nucleophilic displacement reactions of phosphorus esters is discussed.

In light of the demonstrated stability[1-3] of pentacoordinated phosphorus compounds containing alkoxy or aryloxy and carbon ligands (oxyphosphoranes[1]), analogous species containing a hydroxy ligand[4] must be considered as probable intermediates in displacement reactions at phosphorus in phosphorus esters. However, these hydroxyphosphoranes differ from the isolated aryl- or alkyloxyphosphoranes in that they have a facile route for decomposition (eq 1). Thus, at best, they would be unstable intermediates.



Several workers have obtained indirect evidence that such intermediates are formed in reactions of cyclic phosphorus esters and that they have sufficient stability to undergo pseudorotation[5] prior to or competitive with product formation. In the hydrolysis of five-membered ring phosphorus esters,[2,7] the product ratios obtained have been explained by formation of a phosphorane intermediate which may undergo pseudorotation or directly decompose to products, depending on the system. The retention of configuration[8,9] observed in the transesterification of four-membered ring esters (phosphetanes) has been credited to the formation of the cyclic phosphorane, pseudorotation, and decomposition to products. Pseudorotation has also been invoked in the hydrolysis[10] of these phosphetane esters.

In contrast to cyclic esters, there seems to be little information that reactions of acyclic esters involve intermediates of any detectable degree of stability. It has been argued[1a,2b] that acyclic oxyphosphoranes are less stable than cyclic oxyphosphoranes containing a five-membered ring; while the reverse order of stability is observed in the tetracoordinated phosphorus esters. These stability differences may imply that the

(1) (a) F. Ramirez, *Accounts Chem. Res.*, **1**, 168 (1968); (b) F. Ramirez, *Bull. Soc. Chim. Fr.*, 3491 (1970).

(2) (a) F. H. Westheimer, *Accounts Chem. Res.*, **1**, 70 (1968), and references therein; (b) E. A. Dennis and F. H. Westheimer, *J. Amer. Chem. Soc.*, **88**, 3432 (1966).

(3) (a) D. B. Denney, D. Z. Denney, B. C. Chang, and K. L. Marsi, *ibid.*, **91**, 5243 (1969); (b) D. B. Denney and D. H. Jones, *ibid.*, **91**, 5821 (1969); (c) B. C. Chang, W. E. Conrad, D. B. Denney, D. Z. Denney, R. Edelman, R. L. Powell, and D. W. White, *ibid.*, **93**, 4004 (1971).

(4) Oxyphosphoranes containing one or more hydroxy ligands (OH or O^-) will be referred to as hydroxyphosphoranes.

(5) For the purpose of this paper, the term "pseudorotation" will refer to an intramolecular ligand exchange in phosphoranes where the two apical ligands are exchanged with two equatorial ligands; the stereochemistry being that predicted by the Berry mechanism.[6]

(6) R. S. Berry, *J. Chem. Phys.*, **32**, 933 (1960).

(7) (a) R. Kluger, F. Covitz, E. Dennis, L. D. Williams, and F. H. Westheimer, *J. Amer. Chem. Soc.*, **91**, 6066 (1969); (b) R. Kluger and F. H. Westheimer, *ibid.*, **91**, 4143 (1969).

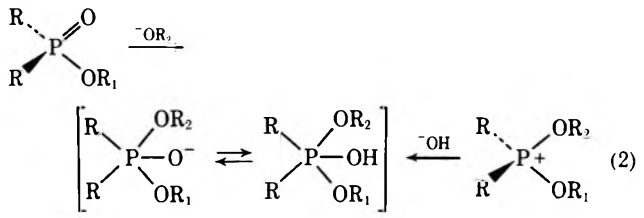
(8) S. E. Cremer and B. C. Trivedi, *ibid.*, **91**, 7200 (1969).

(9) K. E. DeBruin and J. J. Jacobs, *Chem. Commun.*, 59 (1971).

(10) B. W. Hawes and S. Trippett, *ibid.*, 578 (1968).

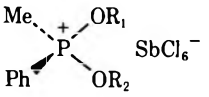
more exothermic decomposition of an acylic hydroxyphosphorane to an acyclic ester would have a relatively lower barrier for reaction, allowing pseudorotation to compete less favorably. As recently as 1968, authors[11] have argued against the existence of intermediates in nucleophilic displacements at acyclic phosphoryl[12] and thiophosphoryl[13] centers on the basis of labeling experiments. More recently, however, it has been reported that the hydrolysis of phosphonothioates[14,15] proceeds with lack of stereospecificity and may be attributed to the formation of a phosphorane intermediate with sufficient lifetime to undergo pseudorotation.

Indirect evidence that certain acyclic hydroxyphosphoranes do exist and have sufficient stability to be detected by virtue of their stereochemical nonrigidity[16] has been obtained from a study of the alkaline hydrolysis of dialkoxyphosphonium salts.[17] From a product analysis in the hydrolysis of (*R*)- and (*S*)-ethoxymenthoxymethylphenylphosphonium hexachloroantimonate, (*R*)- and (*S*)-**1**,[18] it was concluded that pseudorotation of the initially formed hydroxyphosphorane was competitive with direct loss of an alkoxy group to form the product phosphinate esters. The intermediate hydroxyphosphorane in this reaction contains the same ligands as the intermediate formed in the transesterification of a phosphinate ester (eq 2).

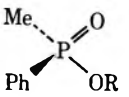


(2)

We decided to investigate the hydrolysis of two other dialkoxyphosphonium salts in order to probe the importance of factors such as steric and electronic effects on pseudorotation or decomposition barriers and to subsequently define the dividing line where pseudorotation becomes noncompetitive with product formation. The hydrolysis of dialkoxyphosphonium salts is a particularly good system for evaluating these factors, since the competition allows an evaluation of the relative energy barriers for pseudorotation *vs.* loss of alkoxide. Also, the product esters are configurationally stable to the reaction conditions. The dialkoxyphosphonium salts investigated in this paper are (*R*)- and (*S*)-menthoxymethoxymethylphenylphosphonium hexachloroantimonate, (*R*)- and (*S*)-**2**,[18] and ethoxymethoxymethylphenylphosphonium hexachloroantimonate (**3**). Phosphonium salts (*R*)- and (*S*)-**2** were chosen to determine the effect of the leaving ability of the nonbulky alkoxide and **3** was chosen to define the importance of steric effects postulated for the hydrolysis of (*R*)- and (*S*)-**1**.



(*S*)-**1**, R_1 = Et; R_2 = Men
(*R*)-**1**, R_1 = Men; R_2 = Et
(*S*)-**2**, R_1 = Me; R_2 = Men
(*R*)-**2**, R_1 = Men; R_2 = Me
(*S*)-**3**, R_1 = Me; R_2 = Et
(*R*)-**3**, R_1 = Et; R_2 = Me



(*S*)-**4**, R = Men
(*S*)-**5**, R = Me
(*S*)-**6**, R = Et

Results

Diastereomerically pure (*S*)-**2** was prepared by O-methylation of menthyl (*S*)-methylphenylphosphinate,[19] (*S*)-**4**. Reaction of (*S*)-**2** with 0.05 *M* NaOH in 50% v/v H_2O–dioxane for 1 min at room temperature afforded phosphinate ester products in greater than 80% yield. These products were identified as (*S*)- and (*R*)-**4** and (*S*)- and (*R*)-mentyl methylphenylphosphinate (**5**). Similarly, diastereomerically pure (*R*)-**2**, prepared by O-methylation of (*R*)-**4**,[19] was hydrolyzed under the same conditions to yield (*S*)- and (*R*)-**4** and (*S*)- and (*R*)-**5**. The ratio of the products from (*S*)-**2** differed from that obtained from (*R*)-**2**, indicating that stereochemical equilibration had not occurred prior to product formation.

The synthesis of (*S*)-**3** was accomplished by O-methylation of (*S*)-ethyl methylphenylphosphinate,[17] (*S*)-**6** (80% optically pure). When this sample of (*S*)-**3** was submitted to the same conditions used in the alkaline hydrolysis of (*S*)- and (*R*)-**2**, the phosphinate ester products consisted of **6** [48% optically pure with the predominance of the *R* isomer] and **5** [78% optically pure (*S*)-**5**]. It follows that optically pure (*S*)-**3** would yield (*R*)-**6** of 60% optical purity and (*S*)-**5** of 98% optical purity. Table I summarizes the results of the hydrolyses.

TABLE I
PRODUCTS OBTAINED FROM THE ALKALINE HYDROLYSIS OF DIALKOXYPHOSPHONIUM SALTS

	Yield of product, %,[a] from hydrolysis of		
Product	(*S*)-**2**	(*R*)-**2**	(*S*)-**3**[b]
(*S*)-**4**	55	32	
(*R*)-**4**	24	42	
(*S*)-**5**	21	8	37
(*R*)-**5**	0	18	1
(*S*)-**6**			12
(*R*)-**6**			50

[a] Per cent of total phosphinate ester products. Standard deviation of five determinations *ca.* 2%. Corrected for differential hydrolysis. [b] Corrected to optically pure phosphonium salt.

Under the reaction conditions for alkaline hydrolysis of the phosphonium salts, **2** and **3**, the product esters are partially hydrolyzed further to methylphenylphosphinic acid. A differential rate of hydrolysis changes the mole ratios of these products. The observed product ratios were corrected for this effect by submitting a known mixture of two phosphinate esters (A and B) to the same conditions used in the alkaline hydrolysis of the phosphonium salts and observing the ratio of

(11) M. J. Gallagher and I. D. Jenkins in "Topics in Stereochemistry," Vol. III, E. L. Eliel and N. L. Allinger, Ed., Interscience, New York, N. Y., 1968, p 31.
(12) M. Green and R. F. Hudson, *Proc. Chem. Soc.*, 307 (1962).
(13) J. Michalski, M. Mikolajczyk, A. Halpern, and K. Proszynska, *Tetrahedron Lett.*, 1919 (1966).
(14) J. Michalski, M. Mikolajczyk, and J. Omelanczuk, *ibid.*, 3565 (1968).
(15) L. P. Reiff, L. J. Szafraniec, and H. S. Aaron, *Chem. Commun.*, 366 (1971).
(16) K. Mislow, *Accounts Chem. Res.*, **3**, 321 (1970).
(17) K. E. DeBruin and K. Mislow, *J. Amer. Chem. Soc.*, **91**, 7393 (1969).
(18) Configurational notation (*R*) and (*S*) refer to chirality at phosphorus. The menthoxy group is derived from (−)-menthol (MenOH).
(19) O. Korpiun, R. A. Lewis, J. Chickos, and K. Mislow, *J. Amer. Chem. Soc.*, **90**, 4842 (1968).

the two esters as a function of time. The difference in the pseudo-first-order rate constants ($k_A - k_B$) was obtained by eq 3, where A_t and B_t represent the

$$\ln\left(\frac{A_t}{A_0}\frac{B_0}{B_t}\right) = -(k_A - k_B)t \quad (3)$$

concentration of esters A and B at time t, respectively. Thus, under the reaction time of 1 min for the hydrolysis of the phosphonium salts, (*S*)- and (*R*)-**2** and **3**, the product ratio of the two esters, **4** and **5** from **2** or **5** and **6** from **3**, deviates from the true product ratio by the exponential term in eq 4. Table II summarizes

$$\frac{A_0}{B_0} = \frac{A_t}{B_t}e^{+(k_A - k_B)t} \quad (4)$$

Table II

Differential Hydrolysis Rates of Phosphinate Esters[a] at 25°

Ester A	Ester B	[NaOH] M	$k_A - k_B$, sec^{-1}	$e^{+(k_A - k_B)60}$
6	4	0.5[b]	1.6×10^{-3}	1.10 (0.010)[c]
6	4	0.05	1.6×10^{-4}	1.01 (0.001)
5	4	0.05	1.4×10^{-3}	1.09 (0.009)
5	6	0.05	1.2×10^{-3}	1.07 (0.007)
5	6	0.5	1.3×10^{-2}	2.18 (0.140)

[a] 50% v/v aqueous dioxane. Pseudo-first-order rate constants. Standard deviation of three determinations is ±5%. [b] Reference 17. [c] Error in parentheses.

the results of this study. As previously pointed out,[17] (*S*)-**4** and (*R*)-**4** are either hydrolyxed at the same state or not hydrolyzed under the reaction time. The results in Table I are corrected for any differential hydrolysis which may have occurred.

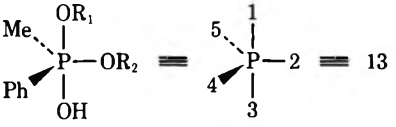
Haake and coworkers[20] have observed, under slightly different conditions, that the methyl ester of diphenylphosphinic acid or diethylphosphinic acid is hydrolyzed about ten times faster than the ethyl ester and from 100 to 300 times faster than the isopropyl ester. Thus, to a first approximation, the difference in rate constants (Table II, $k_A - k_B$) is equal to the rate constant for the hydrolysis of A. Our results are consistent with those of Haake.[20]

The hydrolyses of (*R*)- and (*S*)-**1** were previously carried out[17] using 0.5 *M* NaOH in 50% v/v H_2O–dioxane. As Table II shows, only a 10% correction is needed to account for any differential hydrolysis of the product esters, **6** and **4**. However, this base concentration results in a substantial hydrolysis of the methyl phosphinate, **5**. The lower base concentration of 0.05 *M* NaOH was used in the above hydrolyses to minimize the error resulting from correcting for a differential hydrolysis rate. Since a direct comparison of the product ratios from the respective hydrolyses is desired, the hydrolysis of (*S*)- and (*R*)-**1** was repeated using 0.05 *M* NaOH. Within error, the same product ratios were obtained, after correction, as were previously reported[17] for the hydrolysis in 0.5 *M* NaOH.

Discussion

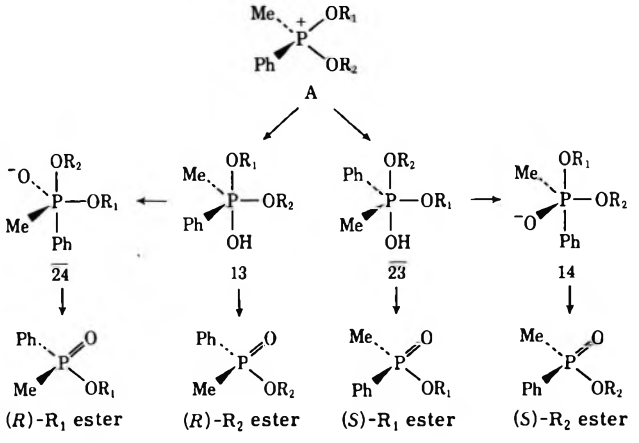
The alkaline hydrolysis of acyclic alkoxyphosphonium salts has been shown[17] to proceed, in general, by attack of hydroxide on phosphorus with resultant cleavage of a P–O bond and loss of alkoxide. In the case of unsymmetrical dialkoxyphosphonium salts, two phosphinate esters can be formed from cleavage of either alkoxy group. For the three chiral acyclic dialkoxyphosphonium salts studied in this paper, (*R*)-**2**, (*S*)-**2**, and **3**, as well as the two previously studied,[17] (*R*)-**1** and (*S*)-**1**, this hydrolysis proceeds with varying lack of stereospecificity. Presumably, attack of hydroxide ion on the dialkoxyphosphonium salt forms a hydroxyphosphorane which has sufficient lifetime to undergo pseudorotation prior to or competitive with loss of alkoxide to form products. Since each phosphonium salt yields products of different degrees of loss of stereospecificity, pseudorotation can be only competitive with product formation. From a product analysis, steric and electronic effects on this competition are obtainable as discussed below.

Phosphoranes and Pseudorotations.—In an earlier paper,[17] the general scheme for the alkaline hydrolysis of a dialkoxyphosphonium salt was developed. For the present discussion, the ligands of the phosphorane intermediates will be numbered as indicated by the equality below. The respective isomers will be noted by a two-digit number referring to the apical ligands of the phosphorane.[21]



Since the preferred mode of reaction of hydroxide on a phosphonium salt is assumed to involve apical attack,[2,16,21] the initially formed phosphoranes from attack on a dialkoxyphosphonium salt of the general structure A would be 13 and $\overline{23}$ (Scheme I). These

Scheme I



phosphoranes can either directly lose the apical alkoxy group (OR_1 from 13 and OR_2 from $\overline{23}$) or undergo pseudorotation by the lowest energy pathway to $\overline{24}$ and 14, respectively.[22] Thus, the general scheme for

(20) (a) P. Haake, C. E. Diebert, and R. S. Marmor, *Tetrahedron Lett.*, 5247 (1968); (b) P. Haake, R. D. Cook, W. Schwarz, and R. R. McCoy, *ibid.*, 5251 (1968).

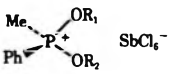
(21) K. E. DeBruin, K. Naumann, G. Zon, and K. Mislow, *J. Amer. Chem. Soc.*, **91**, 7031 (1969).

(22) Pseudorotations of 13 and $\overline{23}$ to $\overline{24}$ and 14, respectively, is assumed to be of lower energy than pseudorotations to 25 and $\overline{15}$, since the former have the more electronegative phenyl group in an apical position.[2,16,23] Even if these energetics were reversed, the conclusions in this paper would hold. Further pseudorotations are assumed to be insignificant, since the first pseudorotation is only competitive with direct loss of alkoxide and additional pseudorotations would require the formation of less stable phosphoranes.[17]

(23) E. L. Muetterties and R. A. Schunn, *Quart. Rev., Chem. Soc.*, **20**, 245 (1966).

TABLE III

PRODUCTS FROM THE ALKALINE HYDROLYSIS OF DIALKOXYPHOSPHONIUM SALTS



			Products						
			—R_1 Ester—		—R_2 Ester—				
R_1	R_2	Confn	(*R*)	(*S*)	(*R*)	(*S*)	(*R*)-R_1 / (*R*)-R_2	(*S*)-R_2 / (*S*)-R_1	(*R*)/(*S*)
Me	Et	(*S*)-**3**	1	37	50	12	0.02 (0.04)[a]	0.33 (0.05)	1.0 (0.2)
Et	Me	(*R*)-**3**[b]	12	50	37	1	0.35 (0.05)	0.02 (0.04)	1.0 (0.2)
Me	Men	(*S*)-**2**	0	21	24	55	(0)	2.6 (0.4)	0.3 (0.1)
Men	Me	(*R*)-**2**	42	32	18	8	2.3 (0.4)	0.25 (0.05)	1.5 (0.3)
Et	Men	(*S*)-**1**[c]	2	38	20	40	0.1 (0.1)	1.0 (0.2)	0.3 (0.05)
Men	Et	(*R*)-**1**[c]	39	27	26	8	1.5 (0.2)	0.3 (0.1)	1.8 (0.4)

[a] Error estimates in parentheses based on a standard deviation of 2% in the product percentages. [b] Calculated assuming enantiomers have identical energies in an achiral medium. [c] Reference 18.

the hydrolysis of dialkoxyphosphonium salts is shown in Scheme I.

The observation of (*R*)-R_1 ester and (*S*)-R_2 ester in the hydrolysis of phosphonium salts **2** and **3** (Table I) requires pseudorotation of the initially formed phosphoranes if loss of alkoxide proceeds from an apical position. Thus, the amount of either of these esters will reflect the fraction of the initially formed phosphorane which does not directly lose an alkoxy group, *i.e.*, the degree to which pseudorotation followed by loss of alkoxide competes with direct decomposition. It would be useful, for predictive reasons, to know the nature of the hydroxy ligand (*e.g.*, OH or O^-) in the initially formed phosphoranes, **13** and $\overline{23}$, as well as phosphoranes **14** and $\overline{24}$ and the energy surface connecting them. Westheimer and coworkers[7] have estimated the pK_a of a hydroxyphosphorane containing only oxygens attached to phosphorus to be *ca.* 9 by the empirical method of Branch and Calvin.[24] This value was consistent with a pH profile plot in their product analysis of the hydrolysis of a cyclic phosphate ester. A similar estimate of the pK_a of a phosphorane containing a phenyl and a methyl ligand such as in **13** or $\overline{23}$ would be *ca.* 12, which is in the region of the base concentration used in the above hydrolysis of the phosphonium salts (0.05 *M* NaOH in 50% aqueous dioxane). This empirical equation does not account for any differences in the pK_a of a phosphorane containing the hydroxy group in an apical *vs.* an equatorial position. Although some difference is expected, the magnitude is unknown. For the present discussion, we will assume that the OH group is in the form which satisfies the electronic requirement[2,23] of its position in the trigonal bipyramidal phosphorane, OH in the apical position and O^- in the equatorial position. The formal mechanism for conversion of a phosphorane containing an apical OH ligand (*e.g.*, **13**) to a phosphorane containing an equatorial O^- ligand (*e.g.*, $\overline{24}$) may either involve a two-step process with ionization prior to or following pseudorotation or a general base catalyzed reaction involving simultaneous proton abstraction and pseudorotation. No information exists on this question; however, if proton transfers are much faster than pseudorotation, the latter mechanism would be more likely since these transfers will be occurring as the energy pathway for pseudorotation is being traversed.

Steric Constraints on Phosphorane Formation.—The products from the hydrolysis of the dialkoxyphosphonium salts investigated in this paper, (*R*)- and (*S*)-**2** and **3**, are listed in generalized form in Table III, along with the previous results for (*R*)- and (*S*)-**1**. That there exists a steric effect on the transition state for formation of the initially formed hydroxyphosphoranes **13** and $\overline{23}$ can be substantiated by contrasting the *R* to *S* product ratio obtained from **1** and **2** to that obtained from **3** (see the last column in Table III). As shown in Scheme I, *R* products can only arise from **13**, the hydroxyphosphorane resulting from attack of hydroxide in the face of the tetrahedral phosphonium salt opposite the OR_1 ligand, while the *S* products can only originate from attack opposite ligand OR_2 with formation of $\overline{23}$. The ratio *R*/*S* is greater than 1 when R_1 is a menthyl group, whereas this ratio is less than 1 when R_2 is the menthyl group.[25] In contrast, when the alkoxy groups are methoxy and ethoxy (**3**), the amount of products arising from the two pathways is similar. Clearly, the bulky menthoxy group influences the partitioning between the two pathways. The magnitude of this steric effect, however, is small, ranging from a 1.5- to a 3-fold preference for attack opposite a menthoxy group, compared to attack opposite a primary alkyl group.

The similar ratios of *R*/*S* from **2** and **1** require the rate-limiting steps for formation of *R* products and *S* products, respectively, to be relatively insensitve to a change in OR_1 (or OR_2) from methoxy to ethoxy. Of the various possibilities, phosphorane formation from the phosphonium salt is the most consistent with this observation. Although loss of an alkoxy group from the hydroxyphosphorane (**13** or $\overline{23}$) to form a hydroxyphosphonium salt should not differ greatly in energetics from loss of hydroxide to return to staring phosphonium salt, an alternate pathway involving the simultaneous abstraction of the proton with loss of the alkoxy group and formation of the P=O bond may be of lower energy. If this were the case, attack of hydroxide would be the rate-limiting step and the observed effect of the menthoxy group is a steric hindrance to approach of the attacking hydroxide.[26]

Steric and Electronic Effects on Pseudorotations and Product Formation.—From Table III, direct information on the degree of pseudorotation *vs.* loss of alkoxide of the initially formed phosphoranes **13** and $\overline{23}$ can be obtained by examining the product distribution. Since

(24) G. E. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice-Hall, New York, N. Y., 1941, p 204.

(25) That these ratios from (*S*)-**2** *vs.* (*R*)-**2** or from (*S*)-**1** *vs.* (*R*)-**1** are not the exact inverse of each other has its origin in the chiral menthoxy group. In both cases, the phosphonium salt with the (*S*) configuration at phosphorus has the greater hindrance for approach of hydroxide.

(26) At present, we have been unable to develop conditions for kinetic measurements to test this postulate.

(*R*)-R_1 ester can only result after one pseudorotation of 13, a comparison of the product ratio, (*R*)-R_1 to (*R*)-R_2 ester, reflects the relative rates of pseudorotation compared to alkoxide loss to form products. Similarily, the ratio of (*S*)-R_2 to (*S*)-R_1 ester represents the competition from 23. These ratios are given in Table III. In Table IV,[27] the results are tabulated in a form which

Table IV

Effect of the Alkoxy Ligands on the Products Derived from 13

13, R_1	(*R*)-R_1/(*R*)-R_2[a] R_2 = Me	R_2 = Et	R_2 = Men	Rel ratio[b]
Me		0.02	(0)	1.0
Et	0.33		0.1	10
Men	2.3	1.5		70
Rel ratio[b]	1.0	0.6	0.3	

[a] See Table III. [b] See text for definition.

facilitates the discussion of factors influencing the competition between the two possible pathways for product formation from 13. The relative ratios in the last column and in the bottom row represent the relative competition between formation of (*R*)-R_1 *vs.* (*R*)-R_2 from 13 as a function of a change in R_1 or R_2, respectively.

Three factors can be postulated to have an influence on the product ratios obtained: (1) the leaving ability of the alkoxide group; (2) electronic effects on the alkoxy ligand which remains attached to phosphorus in the product on the decomposition rates; and (3) steric and electronic effects on pseudorotation rates.

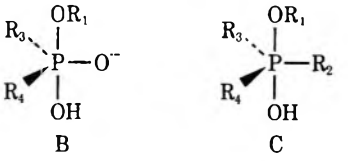
For any given R_2 group, the relative amount of product ((*R*)-R_2) resulting from direct loss of alkoxide (OR_1) decreases as R_1 is changed from methyl to ethyl to menthyl (the ratio of (*R*)-R_1 ester to (*R*)-R_2 ester increases from 1 to 10 to 70). In contrast, when R_1 is constant and R_2 is varied, the reverse order is observed (from 1 to 0.6 to 0.3). The relative order and magnitude in each of these two series is consistent with an inductive effect on the decomposition of 13 to (*R*)-R_2 ester. In the transition state for this reaction, the positive charge on phosphorus is increasing with a corresponding negative charge developing on the alkoxy leaving group. As might be expected, the effect of substituents in the leaving group is greater than that in the remaining alkoxy group. For this system, when the leaving group is methoxide, pseudorotation is virtually noncompetitive with direct decomposition.

Although steric factors were originally proposed to influence the barriers for pseudorotations in these systems,[17] the above order of reactivity does not require this hypothesis. If the "bulky" menthoxy group preferred to occupy an equatorial position, an abnormally low value (*R*)-R_1 ester/(*R*)-R_2 ester would be expected when R_2 is menthyl, while this ratio should be abnormally high when R_1 is menthyl. This behavior is not observed and suggests that the bulk of the menthyl group is sufficiently removed from the crowded phosphorus to exhibit little positional preference around the hydroxyphosphorane. Steric effects on pseudorotational barriers have nicely explained the chemistry of several systems[17,28,29] where a *tert*-butyl group is directly attached to phosphorus; however, in those cases, the crowding around phosphorus would be much more severe.

An alternate explanation for the above suggested lack of steric constraints on pseudorotational barriers is that both pseudorotation and decomposition barriers are affected to the same amount and therefore, not detectable by this study. Loss of alkoxide from 13 should be accelerated due to relief of strain when a menthoxy group is the leaving group (R_1) as well as when the menthoxy group is equatorial (R_2). Pseudorotations should be accelerated when the menthoxy group is apical and slowed down when it is equatorial. Thus, the steric effect may be nonobservable when R_1 is menthyl but should be magnified when R_2 is menthyl. Since this behavior is not observed, steric effects on positional preferences by a menthoxy group on a phosphorane must be small.

In summary, the fate of a phosphorane such as 13 in terms of its ability to undergo psuedorotation competitively with direct loss of an alkoxide group is determined primarily by the leaving ability of the alkoxide and, to a lesser extent, by electronic effects of the ligands which remain attached to the phosphorus. In the above system, when methoxide is the leaving group, pseudorotation is virtually noncompetitive. Also, in order for a bulky ligand to originate conformational preferences in a phosphorane, as measured by relative rates of pseudorotation, the bulk of the ligand must, apparently, be similar to that of a *tert*-butyl group.

Pseudorotation in Reactions of Phosphorus Esters.—If one assumes that nucleophilic displacement reactions at phosphorus in acyclic phosphorus esters proceed through the intermediacy of a phosphorane, and that axial attack is preferred over equatorial attack, the initially formed phosphorane would have the nucleophile and the most electronegative group in the apical positions. In alkaline hydrolyses, the hydroxyphosphoranes would have the general structure B. An



B C

analogous intermediate (C) would be formed in the alkaline hydrolysis of alkoxyphosphonium salts, the difference being only in the replacement of the electropositive oxy ligand (O^-) by an electropositive alkyl or aryl group (R_2). Granted that the transition state for loss of alkoxide may be stabilized by resonance when the phosphorane contains the oxy ligand compared to an alkyl or aryl ligand, the degree to which an initially formed phosphorane may undergo pseudorotation is at a maximum in the hydrolysis of alkoxyphosphonium salts, other things being equal.

It has been shown[30] that the alkaline hydrolysis of an acylic monoalkoxyphosphonium salt, ethoxymethyl-

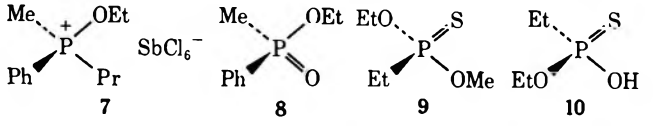
(27) Table IV and future discussion will be concerned only with the products derived from 13. The transition state for loss of alkoxide (OR_1) from 13 (R_2 = menthyl) has the same relative configuration of phosphorus and the menthyl group as the transition state for attack of hydroxide on (*R*)-**1** or (*R*)-**2**, the diastereomers which gave the least steric hindrance for formation of the phosphorane. Thus, steric constraints on decomposition are minimized.

(28) A. P. Stewart and S. Trippett, *Chem. Commun.*, 1279 (1970).

(29) D. Z. Denney, D. W. White, and D. B. Denney, *J. Amer. Chem. Soc.*, **93**, 2066 (1971).

(30) G. Zon, K. E. DeBruin, K. Naumann, and K. Mislow, *ibid.*, **91**, 7023 (1969).

phenylpropylphosphonium hexachloroantimonate (**7**), proceeds stereospecifically with inversion of configuration. Any pseudorotation of the initially formed phosphorane (C, R_2 = Pr; R_3 = Me; R_4 = Ph) requires exchanging the apical hydroxy and alkoxy groups for two electropositive groups, a process noncompetitive with direct loss of an alkoxide. Extension of this argument to the hydrolysis of an acyclic phosphinate ester (*e.g.*, ethyl methylphenylphosphinate, **8**), would predict that no pseudorotation of the intermediate



phosphorane (B, R_3 = Me; R_4 = Ph) would occur prior to product formation. The absence of any ^{18}O exchange into the phosphoryl oxygen of recovered starting material[20] when the hydrolysis is carried out in $H_2{}^{18}O$ is consistent with this prediction in that the phosphoryl oxygen and the hydroxide oxygen cannot assume identical environments if pseudorotation is blocked.

A similar extension of the results in this paper to the hydrolysis of acyclic phosphonate esters would suggest that pseudorotation of the initially formed phosphorane would only be competitive with loss of alkoxide when the leaving group is poorer than methoxide. The stereochemistry of the alkaline hydrolysis of a phosphonothioate, *O*-ethyl *O*-methylethylphosphonothioate (**9**) to *O*-ethylethylphosphonothioic acid (**10**) has been shown[14] to proceed with 85% inversion of configuration. Although labeling experiments were not carried out, the observed stereochemistry was postulated to result from partial C–O bond cleavage.

An alternative explanation would involve competitive formation of two hydroxyphosphoranes with either the methoxy ligand or the ethoxy ligand in the apical position. Direct loss of methoxide from the former and pseudorotation followed by loss of methoxide from the latter would result in the formation of **10** with inversion and retention, respectively. The stereospecificity of the hydrolysis would then be determined by the relative energies of the two pathways. Our results above would indicate that this alternative explanation is indeed possible.

In general, the results of this paper would indicate that nucleophilic displacements of alkoxide in acyclic phosphinate and phosphonate esters by a nucleophile of similar or greater electronegativity, when bonded to phosphorus, than hydroxide (*e.g.*, alkoxide in transesterification reactions) should proceed with little if any pseudorotation of the initially formed phosphorane. Further studies are underway to test the limits of this generalization.

Experimental Section[31]

Synthesis of Dialkoxyphosphonium Hexachloroantimonates. A. (*S*)-Menthoxymethoxymethylphenylphosphonium Hexachloroantimonate [(*S*)-2].—A solution of diastereomerically pure menthyl (*S*)-methylphenylphosphinate, (*S*)-**4** (590 mg, 1.7 mmol), $[\alpha]_D$ −95°, in dichloromethane (10 ml) was added to a heterogenous mixture of trimethyloxonium hexachloroantimonate[32] (600 mg, 1.6 mmol) in dichloromethane (20 ml). The mixture was stirred at room temperature until the solution became homogeneous (15 min) and then stirred for an additional 1 hr. Concentration of the solution under vacuum to 5 ml, followed by addition of this residue to anhydrous ether (100 ml), produced a white, crystalline material (970 mg, 95%), mp 102–103° dec, $[\alpha]_D$ −32° (*c* 3.77, CH_2Cl_2). The pmr spectrum of this material was consistent with that expected for diastereomerically pure (*S*)-**2**, and featured PCH_3 (d, 2.49 δ, J_{PCH} = 14 Hz), $POCH_3$ (d, 4.22 δ, J_{POCH} = 12 Hz).

Anal. Calcd for $C_{18}H_{30}PO_2SbCl_6$: C, 33.58; H, 4.70. Found: C, 33.69; H, 4.67.

B. (*R*)-Menthoxymethoxymethylphenylphosphonium Hexachloroantimonate [(*R*)-2].—The synthesis of (*R*)-**2** from diastereomerically pure (*R*)-**4**, $[\alpha]_D$ −17°, was similar to that of (*S*)-**2**, mp 90–92° (800 mg, 78%). The pmr spectrum of this material featured PCH_3 (d, 2.47 δ, J_{PCH} = 14 Hz), $POCH_3$ (d, 4.07 δ, J_{POCH} = 12 Hz). By analysis of the $POCH_3$ region of the pmr spectrum, (*R*)-**2** was found to be diastereomerically pure.

C. (*S*)-Ethoxymethoxymethylphenylphosphonium Hexachloroantimonate [(*S*)-3].—A solution of (*S*)-ethyl methylphenylphosphinate [(*S*)-**6**] (1.0 g, 5.4 mmol), $[\alpha]_D$ −36° (80% optically pure) in dichloromethane (10 ml) was added to a heterogeneous mixture of trimethyloxonium hexachloroantimonate (2.1 g, 5.4 mmol) in dichloromethane (20 ml) and stirred at room temperature for 4 hr. After 1 hr, the solution was homogeneous. Addition of this solution to anhydrous ether (100 ml) produced a white, crystalline material which was identified as (*S*)-ethoxymethoxymethylphenylphosphonium hexachloroantimonate[(*S*)-**3**] (2.5 g, 86%), mp 104–106° dec. The pmr spectrum (CH_2Cl_2) of this material featured PCH_3 (d, 2.30 δ, J_{PCH} = 14 Hz), $POCH_3$ (d, 4.07 δ, J_{PCCH} = 12 Hz), $POCH_2CH_3$ (apparent quintet, 4.42 δ, J_{POCH} = 7 Hz), $POCH_2CH_3$ (t, 1.47 δ, J_{HCCH} = 7 Hz).

Anal. Calcd for $C_{10}H_{15}PO_2SbCl_6$: C, 22.51; H, 3.02; P, 5.80. Found: C, 22.89; H, 3.25; P, 5.72.

Hydrolysis of Dialkoxyphosphonium Hexachloroantimonates. A. (*S*)- and (*R*)-Menthoxymethoxymethylphenylphosphonium Hexachloroantimonates [(*S*)- and (*R*)-2].—The hydrolyses of (*S*)-**2** and (*R*)-**2** were carried out by the identical procedure used in the hydrolysis of (*S*)-**1** and (*R*)-**1**[17] except that 0.05 *M* NaOH was used instead of 0.5 *M* NaOH. A solution (100 ml) of 0.05 *M* NaOH in 50% v/v aqueous dioxane was added to a solution of either (*S*)-**2** or (*R*)-**2** (300 mg, 5 mmol) in dioxane (0.5 ml), and the heterogeneous mixture was stirred for 1 min. The reaction mixture was extracted with dichloromethane and the combined organic layers were dried (magnesium sulfate). Removal of solvent under reduced pressure gave a mixture of (*S*)- and (*R*)-**4**, methyl methylphenylphosphinate (**5**), and *l*-menthol. The total products (*ca.* 100 mg) from the hydrolysis of (*S*)-**2** or (*R*)-**2** were analyzed as follows.

The PCH_3 group in each of the three products from hydrolysis of **2** [(*S*)-**4**, (*R*)-**4**, and **5**] has a characteristic signal in the pmr spectrum: (*S*)-**4**, 1.66 δ, J_{PCH} = 14.5 Hz; (*R*)-**4**, 1.62 δ, J_{PCH} = 14.5 Hz; and **5**, 1.63 δ, J_{PCH} = 14.5 Hz. The proportions of the three compounds were estimated by comparing peak heights of the upfield half of each doublet. The relative amounts of **4** and **5** were estimated by glpc analysis (6 ft, SE-30, 200°) of the crude mixture of products from the hydrolysis of (*S*)-**2** and (*R*)-**2**, and compared to the pmr results.

Pure samples of **4** and **5** were obtained by collection from a gas chromatograph. The entire peak corresponding to each compound was collected. The ratio thus obtained agreed well (within 2%) with that determined on the crude mixture.

The optical purity and absolute configuration of **5** was established by its conversion to methyl-β-naphthylphenylphosphine oxide (**7**) with β-naphthylmagnesium bromide.[17] A sample of **5**, $[\alpha]_D$ −21° yielded (*S*)-**7**, $[\alpha]_D$ +11° (chloroform). Thus, this sample of **5** was 40% optically pure based on the highest reported rotation of **7**, with a predominance of the *S* isomer, granted that the Grignard reaction proceeded with complete retention of configuration.[19] It follows that optically pure **5** would have an absolute rotation of 52°. The hydrolysis of diastereomerically

(31) Elemental analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. Pmr spectra were recorded on a Varian A-60A spectrometer and refer to *ca.* 10% solution in deuteriochloroform, with tetramethylsilane as internal standard. Chemical shifts are reported in parts per million from TMS. Optical rotations were measured on a PE-141 polarimeter and refer to solvent benzene (c 1–3 g/100 ml), except as noted.

(32) H. Meerwein, E. Battenberg, H. Gold, E. Pfeil, and G. Willfang, *J. Prakt. Chem.*, **154**, 83 (1939).

pure (*S*)-2 gave **5**, $[\alpha]_D$ −52° which would correspond to optically pure **5** of the *S* configuration.

The sample of **5**, $[\alpha]_D$ +19.7°, obtained from hydrolysis of (*R*)-2 is therefore 38% optically pure with the predominance of the *R* isomer.

B. (*S*)-Ethoxymethoxymethylphenylphosphonium Hexachloroantimonate [(*S*)-3].—The hydrolysis of (*S*)-**3** (80% optically pure) was carried out by the identical procedure used for the hydrolysis of (*S*)- and (*R*)-**2**. A mixture of methyl methylphenylphosphinate (**5**) and ethyl methylphenylphosphinate (**6**) was obtained and analyzed by pmr and glpc for relative amounts. The two phosphinate esters, **5** and **6**, were separated by glpc (6 ft, SE-30, 150°) to give **5**, $[\alpha]_D$ −40° (77% optically pure), and **6**, $[\alpha]_D$ +22° (48% optically pure[17]). Thus, optically pure (*S*)-**3** would give, upon hydrolysis, a ratio of (*S*)-**5** to (*R*)-**5** of 98:2 and a ratio of (*S*)-**5** to (*R*)-**6** of 20:80.

Control Experiments.—That the phosphinate ester products are configurationally stable under the reaction conditions for hydrolysis was shown by submitting a sample of each to these exact conditions. Recovery of unreacted ester after 5 min yielded a product of unchanged stereochemistry.

The product ratios obtained from the hydrolyses of the dialkoxyphosphonium salts were corrected for the differential rate of hydrolysis of the various esters by the following procedure. A mixture of two phosphinate esters (A and B) of known mole per cent ratio was submitted to the conditions of the hydrolyses of the phosphonium salt. Aliquots were taken and quenched by extracting with dichloromethane and the recovered mixture of the two esters was analyzed by pmr. A plot of ln [A/B] against time yielded a slope ($k_A - k_B$, assuming pseudo-first-order kinetics). Table II contains the results of this study.

Registry No.—2, 34630-90-5; (*S*)-**3**, 34630-91-6; (*R*)-**3**, 34630-92-7; **4**, 34638-63-6; (*S*)-**5**, 34647-06-8; (*R*)-**5**, 34647-07-9; (*S*)-**6**, 33642-98-7; (*R*)-**7**, 34638-79-4; (*S*)-**7**, 34630-93-8.

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Three-Membered Rings. III.[1a] Ultraviolet Spectral Evidence of a Stereochemical Bias in Rigid *p*-Nitrophenylcyclopropanes[1b]

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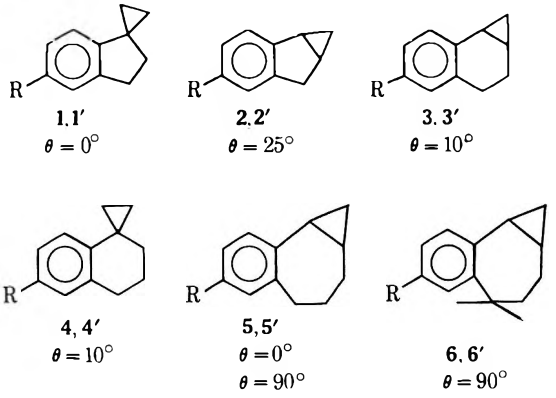
A study of the uv spectra of a series of conformatially rigid *p*-nitrophenylcyclopropanes and the parent hydrocarbons demonstrates the existence of a slight stereochemical bias for electronic interaction between the cyclopropyl group and the nitrobenzene or benzene chromophore. In the series studied, the orientation of the cyclopropane ring deviates from the bisected geometry from 0 to 90°.

The ability of the para-enriched carbon–carbon orbitals of cyclopropane to conjugate with neighboring unsaturated systems has been demonstrated.[2-4] Several recent studies have dealt with the effects of the cyclopropyl substituent on the electronic spectra of π systems.[5-8] Goodman and Eastman[7] studied the uv spectra of a series of rigid phenylcyclopropanes (**1–3**) in order to ascertain the preferred geometry for expression of olefinic character. On the basis of small spectral variations, they concluded that there is no preferred geometry for conjugation of a cyclopropane ring with a phenyl nucleus. Strait, *et al.*,[9] have demonstrated the usefulness of the nitrobenzene chromophore in evaluating the electronic properties of three-membered rings. Hahn and coworkers[8] extended the study of Goodman and Eastman[7] by including **4** and **5** and in addition studied the para-nitro derivatives (**1′–5′**), and concluded that conjugation in cyclopropyl aromatic systems is a detectable function of cyclopropane geometry if the interacting chromophore is sufficiently electron attracting.



1–6, R = H
1′–6′, R = NO_2
θ = Deviation in degrees from bisected geometry

According to Bernett,[10] total overlap between the sp^5 bent bonds of the cyclopropane ring and an adjacent p orbital decrease only slightly for deviations up to 39° (Figure 1B) from the optimum geometry (Figure 1A) and thereafter decreases more rapidly to a minimum at 90° (Figure 1C).

Compound **5** and its nitration products are the most crucial in their study[8] because they represent the only compounds having a large deviation (θ = 90°) from optimum geometry. There are two conformations of **5**; the sterically preferred conformation has the least preferred geometry for orbital overlap (θ = 90°), whereas the sterically less preferred conformation has the optimum geometry for overlap (θ = 0°). It

(1) (a) Paper II: L. A. Strait, D. Jambotkar, R. Ketcham, and M. Hrenoff, *J. Org. Chem.*, **31**, 3976 (1966). (b) Taken in part from the Ph.D. Thesis of L. C. M. Presented, in part, at the 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 12, 1968. (c) U. S. Public Health Service Predoctoral Trainee.

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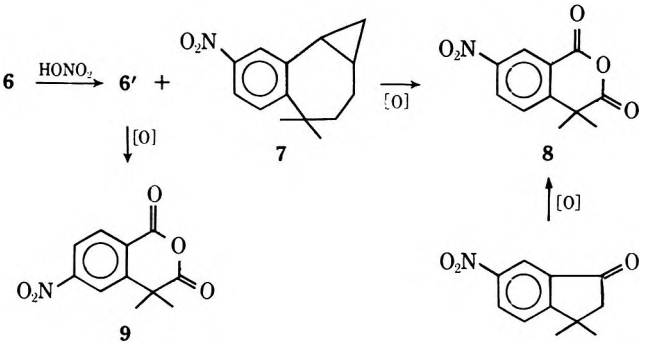
seemed possible that stabilization gained from overlap might significantly overcome the small steric effects so that one could not assume that **5** and especially **5′** would be exclusively in the conformation having $\theta = 90°$. We have chosen to eliminate this uncertainty by introduction of two methyl substituents at C-5 (**6**) which further reduces the stability of the conformation $\theta = 0°$ whereas it has an insignificant effect on the other ($\theta = 90°$), thus ensuring that **6** exists exclusively in the least favored conformation for overlap ($\theta = 90°$).

The cyclopropyl group in **1**–**4** is clearly a stronger ortho, para director than the other alkyl substituents $(CH_2)_n$; however, the weakness of overlap in **5** and **6** permits significant amounts of nitration meta to the cyclopropyl substituent (**7**). The weakness of this interaction also makes spectroscopic structural assignments for the two 1,2,4-trisubstituted products difficult. The two methyl substituents provide a means for an unambiguous chemical determination of structure for these two nitration products, since oxidation of **7** stops at a dimethylhomophthalic acid derivative (**8**) which can be synthesized in an unambiguous fashion.



Results and Discussion

Uv Spectra.—The nitro compounds **1′**–**4′** and **6′** have characteristic nitrobenzenelike uv spectra with absorption maxima ranging from 276 to 290 nm in hexane. The pattern of differences is clearly interpretable, particularly when compared with *p*-nitrophenylcyclopropane, which absorbs at 280 nm in hexane (Table I).

TABLE I

RIGID ARYLCYCLOPROPANES

		Hydrocarbons		Nitro compd	
Compd	θ	λ_{max} (ϵ)[a]	$\Delta\lambda$	λ_{max} (ϵ)[b]	$\Delta\lambda$
1, 1′	0	281 (17.8)	0	290 (9.5)	0
2, 2′	25	278 (13.9)	3	286.5 (9.8)	3.5
3, 3′	10	279 (10.1)	2	287 (10.5)	3
4, 4′	10	277.5 (13.9)	3.5	288 (10.5)	2
6, 6′	90	274.5[d] (2.94)	6.5	276 (10.4)	14
0, 0′[c]		275 (3.8)	6.0	280 (10.9)[e]	10

[a] $^1L_b \leftarrow A^1$, λ_{max} (nm), $\epsilon \times 10^{-2}$, solvent hexane. The same trend was found in the $^1L_a \leftarrow {}^1A$ transition. [b] λ_{max} (nm), $\epsilon \times 10^{-3}$, solvent hexane. [c] 0 and 0′ refers to PhC_3H_5 and *p*-NO_2-PhC_3H_5. [d] The most intense band in the transition is at 262.5 nm, but the 0–0 band should be at about 12 nm longer wavelength (the difference between dimethylbenzosuberane and tetralin). [e] See ref 9.

Small deviations from the optimum geometry give rise to very small spectral changes, whereas the larger value of θ in **6** produces a proportionately larger change as predicted from the suggestion of Bernett.[10] The difference between absorption maxima ($\Delta\lambda$) of **1′** ($\theta = 0°$) and **2′** ($\theta = 25°$) is only 3.5 nm, whereas the $\Delta\lambda$ between **1′** ($\theta = 0°$) and **6′** ($\theta = 90°$) is 14 nm. Thus it is evident from the uv spectra that there is a stereochemical bias for maximum electronic interaction.

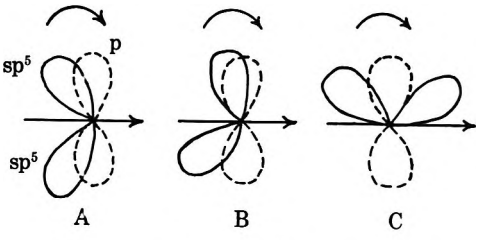


Figure 1.[10]

Review of the spectral data for the hydrocarbons[7,8] with the addition of **6** reveals that a correlation does exist between θ and the uv maxima which parallels that found in the nitro compounds. The uv spectra of 11 substituted indans[11] are very similar to that of indan [λ_{max} 273.2 nm (ϵ 1400)] in contrast to the red shift and intensity increase seen in **1** and **2**. Similar constancy is observed for a series of six substituted tetralins[12] [tetralin λ_{max} = 273.5 nm (ϵ 600)] where, again, introduction of the fused cyclopropyl ring or a spiro cyclopropyl ring produces a significant red shift.

The uv spectrum of 1,1-dimethylbenzosuberane has an absorption maximum (not the 0–0 band) at 261.5 nm (ϵ 1900); introduction of the fused cyclopropyl group (**6**) does not produce a red shift.

Nitration.—Nitration of **1**–**4** leads predominantly to *p*-nitrophenylcyclopropanes (**1′**–**4′**) as indicated by their uv and ir spectra. Glc indicated two minor nitration products which in cases where they were isolated were shown to have the nitro group ortho or meta to the cyclopropyl group. Nitration of **6** gave four products, two major products (1,2,4-trisubstituted benzenes) and two minor products (1,2,3-trisubstituted benzenes). The uv and nmr spectra of the major nitration products of **6** (**6′**, **7**) were so similar that structural assignments could not be made with certainty. Oxidation of **6′** with chromic acid gave **9** while **7** gave **8**. The structure of **8** was confirmed by independent synthesis.

Experimental Section[13]

Spectroscopic Methods.—Uv spectra (Table I) were obtained in spectroquality hexane (Matheson Coleman and Bell) with a Cary Model 14 spectrophotometer. Nmr spectra were obtained in $CDCl_3$ with a Varian A-60A spectrometer using TMS as an internal standard. The ir spectra were recorded with a Perkin-Elmer 337 or 457 spectrophotometer using potassium bromide plates for liquids and potassium bromide pellets for solids.

1-Methyleneindan was synthesized using the procedure of Hahn, *et al.*,[8] with the following modifications. The Wittig reaction was carried out in dry THF under nitrogen. The re-

(11) 1-(2-piperidylmethyl)-1-indanol hydrochloride, 2-bromo-1-indanol, 1-methylindan, 2-methylindan, 1,2-dimethylindan, 1-hexyl-2-butylindan, 1,3-dimethylindan, 1,3,3-trimethyl-1-indanol, 2-decylindan, 1-hexadecylindan, and 2-hexadecylindan.

(12) 1,4-diethyltetralin, 1,1,4,4-tetramethyl-2,3-tetralindiol, 2-methyltetralin, 2-ethyltetralin, 2-butyltetralin, 2-phenyltetralin.

(13) Melting points are taken on a Thomas-Hoover melting point apparatus and are corrected. Gas chromatographic separations were carried out on an Aerograph A90C gas chromatograph. Elemental analyses were performed in the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley.

action was warmed to reflux and allowed to proceed for 32 hr. Wet THF was added, the contents were vacuum filtered, and the filtrate was dried (anhydrous Na_2SO_4). Excess solvent was removed under vacuum. The dark yellow oil thus obtained was chromatographed twice on neutral alumina using hexane to give a colorless oil, bp 95–97° (20 mm) [lit.[7,8] bp 99.5–101.5° (29 mm), 26–28° (0.2 mm)] in 56% yield. Indene obtained from commercial sources was distilled before use.

1,2-Dihydronaphthalene was synthesized by the procedure of Hurd and Juel,[14] bp 90–91° (15 mm) [lit.[14] bp 87–89° (15 mm)].

1-Methylenetetralin was synthesized in 44% yield using the above procedure for 1-methyleneindan except that anhydrous ether was used as the solvent and the reaction was carried out for 15 hr at room temperature and then under reflux for an additional 6 hr. Wet ether was added to destroy the ylide (colorless oil), bp 94–96° (5 mm) [lit.[8,15] bp 58° (0.5 mm), 103° (14 mm)].

5,5-Dimethyl-6,7-dihydro-5*H*-benzocycloheptene.—3-Methyl-3-phenylbutyric acid was prepared from benzene and 3-methylcrotonic acid by the method of Julia, *et al.*,[16] in 86% yield, mp 45–48° (lit.[16,17] mp 57–58°).

The ethyl ester, bp 106–107° (2 mm), prepared with hydrochloric acid and absolute ethanol, was reduced with lithium aluminum hydride to give 86% of 3 methyl-3-phenyl-1-butanol, bp 112° (1 mm) [lit.[13] bp 135° (14 mm)].

3-Methyl-3-phenyl-1-butyl *p*-toluenesulfonate, bp 210° (3 mm), ir (neat) 1370 and 1175 cm^{-1}, was treated with sodiomalonic ester to give diethyl (3-methyl-3-phenylbutyl)malonate in 42% yield, bp 150–170° (3 mm) [lit.[13] bp 150–160° (2 mm)], free acid mp 162–163°.

The diethyl ester (70 g, 0.237 mol) and 60 g of potassium hydroxide in 1000 ml of methanol and 150 ml of water were refluxed for 4 hr. Dilution with ice, acidification with hydrochloric acid, and extraction with chloroform gave on distillation 42.4 g (81%) of the methyl ester, bp 131–162° (6 mm), identical in all respects with the product obtained by stepwise hydrolysis, decarboxylation, and esterification.

Methyl 5-methyl-5-phenylhexanoate (42.2 g, 0.20 mol) in 2.32 kg of polyphosphoric acid was heated on a boiling water bath for 2 hr. The hot reaction mixture was poured onto 4 l. of ice, allowed to stand for 2 hr, and then extracted with ether. The extract was washed with sodium bicarbonate, dried, and concentrated. Vacuum distillation of the residue gave 25.2 g (67%) of 5,5-dimethyl-1-benzosuberone: bp 92° (1 mm) [lit.[13] bp 94–96° (0.3 mm)]; ir 1690 cm^{-1} (C=O); nmr δ 1.30 (s, 6 H, CH_3), 1.80 (m, 4 H, CH_2), 2.68 (m, 2 H, $CH_2C{=}O$), and 7.33 (m, 4 H, C_6H_4).

A stirred solution of the ketone (25 g, 0.134 mol) in methanol was added, in portions, to 2.55 g (0.268 mol) of sodium borohydride in 25 ml of methanol. After stirring for 4 hr water was added and the product was extracted with ether. The ether solution was washed with water, dried, and concentrated. The crude product had an ir band at 3350 cm^{-1} (alcohol).

Acetylation was accomplished by refluxing in acetic anhydride for 4 hr, followed by dilution with water, extraction with ether, and concentration. The residue and 2 g of potassium acid sulfate in a distillation flask were heated at 120° (20 mm) until acetic acid was no longer evolved, then distilled under reduced pressure to give 14.4 g (63%) of 5,5-dimethyl-6,7-dihydro-5*H*-benzocycloheptene: bp 82–83° (1 mm); nmr δ 1.9, 2.25, and 2.7 (m, 2 H each, CH_2), two triplets at 5.8 (J_{CH} = 12, J_{CH_2} = 4 Hz, 1 H, vinyl), and two triplets at 6.3 (J_{CH_2} allylic = 2 Hz, 1 H) and 7 (m, 4 H, C_6H_4).

Anal. Calcd for $C_{13}H_{16}$: C, 90.64; H, 9.36. Found: C, 91.05; H, 9.15.

Spiro[cyclopropane-1,1′-indan] (1), **benzo[*a*]cyclopropa[*c*]cyclopentene(cycloprop[*a*]indene)** (2) **and benzo[*a*]cyclopropa[*c*]cyclohexene(1a,2,3,7b-tetrahydro-1*H*-cycloprop[*a*]naphthalene)** (3) were synthesized according to the procedures of Goodman and Eastman.[7]

Spiro[cyclopropane-1,1′-tetralin] (4).—A suspension of zinc–copper couple[18] (2.7 g), methylene iodide (1.0 g), and a crystal of iodine in 25 ml of ether was stirred under reflux for 30 min. A solution of 4 g of methylene iodide and 4.13 g (0.029 mol) of 1-methylenetetralin was added dropwise over 1 hr. After refluxing for 8 hr, 2.7 g of couple and 5 g of methylene iodide were added and reflux was continued for 40 hr. The solids were removed by filtration through Filteraid and the filtrate was washed three times each with saturated ammonium chloride, 5% ammonium hydroxide, and water. After removal of solvent, the yellow oil (4.34 g) was shown by glc to contain about 50% of desired product. Removal of unreacted starting material by oxidation with $KMnO_4$, followed by chromatography on neutral alumina with petroleum ether (bp 30–60°), yielded pure product having the same nmr spectrum as reported by Hahn, *et al.*[8]

1,1-Dibromo-4,4-dimethylbenzo[*a*]cyclopropa[*c*]cycloheptene.—To a stirred suspension of potassium *tert*-butoxide, prepared from 5.03 g (0.129 mol) of potassium and dry, pure *tert*-butyl alcohol, in 120 ml of pentane was added first a solution of 11.0 g (0.067 mol) of olefin in 30 ml of pentane, then, dropwise, 32.5 g (0.129 mol) of bromoform over a 30-min period. After stirring for 3 hr at 0°, water was added and the phases were separated. The organic phase was dried, the pentane was removed, and the dark yellow residue was distilled, bp 140–142° (0.4 mm), to give 14.9 g (71%) of the product: nmr δ 0.7–1.15 (m, 1 H, cyclopropyl), 1.37 (s, 3 H, CH_3), and 1.48 (s, 3 H, CH_3), two broad singlets at 2.85 and 3.06 (benzylic cyclopropyl), complex multiplets around 1.6 and 2.0 (CH_2 and cyclopropyl), and signals at 7.3 (C_6H_4).

Anal. Calcd for $C_{14}H_{16}Br_2$: C, 48.84; H, 4.68; Br, 46.67. Found: C, 48.82; H, 4.63; Br, 46.38.

4,4-Dimethylbenzo[*a*]cyclopropa[*c*]cycloheptene (6).—To a stirred solution of the dibromo compound (14.9 g, 0.043 mol) in 124 ml of ether was added simultaneously a solution of 161 ml of methanol and 37 ml of water, and 14.2 g of sodium in 0.3-g pieces for a 1-hr period. After stirring over 1 hr, additional aqueous methanol (95 ml) and sodium (11.0 g) were added as above and the mixture was stirred again for 1 hr. Fourfold dilution with water, extraction with ether, and concentration of the dried extract gave a yellow oil which when distilled gave 3.4 g (43%) of the reduced cyclopropane compound, bp 124° (0.5 mm), and 7.0 g of starting dibromide, nmr δ 0.2–2.3 (m, 8 H, aliphatic), 1.38 (s, 3 H, CH_3), 1.61 (s, 3 H, CH_3), and 7.1–7.5 (m, 4 H, aromatic).

Anal. Calcd for $C_{14}H_{18}$: C, 90.26; H, 9.74. Found: C, 90.20; H, 9.78.

5′-Nitrospiro[cyclopropane-1,1′-indan] (1′).—To a stirred solution of 1.85 g (8.0 mmol) of cupric nitrate trihydrate in 20 ml of acetic anhydride at 0° was added 1.1 g (8.0 mmol) of spiro[cyclopropane-1,1′-indan] in 20 ml of acetic anhydride dropwise at a rate so that the temperature did not rise above 7° (about 0.5 hr). The reaction vessel was removed from the ice bath and allowed to stand at 25° for 2 hr. The insoluble salts were removed by filtration and the filtrate was diluted threefold with ice water to hydrolyze the acetic anhydride. The mixture was washed with 5% sodium bicarbonate and water and then dried. Removal of ether gave a yellow oil. Preparative glc on a 0.375 in. × 7 ft column of 20% SE-30 on Diatoport W with nitrogen as a carrier gas, and using traps externally cooled by liquid nitrogen under reduced pressure, gave the desired product.

There were only three components, two of which were collected. The major component had the longest retention time and solidified in the trap. This fraction was chromatographed on neutral alumina using 1:1 ether–petroleum ether. Crystallization from aqueous methanol followed by sublimation gave about 20 mg of a pale yellow solid, mp 82.5–83.5° (lit.[8] mp 81–82.5°).

4-Nitrocycloprop[*a*]indene (2′).—Treating 1 g (8.0 mmol) of 2 with 1.85 g (8.0 mmol) of cupric nitrate and 20 ml of acetic anhydride as described in 1′ gave a similar yellow oil. Preparative glc and chromatography gave 45 mg, mp 76–77° (lit.[8] mp 76–76.5°).

5-Nitro-1a,2,3-7b-tetrahydro-1*H*-cycloprop[*a*]naphthalene (3′).—Hydrocarbon 3 (0.5 g, 4.0 mmol) when nitrated with cupric nitrate trihydrate and purified in the usual way gave about 15 mg of a solid, mp 45.5–46° (lit.[8] mp 45.0–46.5°).

6′-Nitrospiro[cyclopropane-1,1′-tetralin] (4′).—Fuming nitric acid (3.85 g, 0.06 mol) was added to 61 g (0.6 mol) of acetic anhydride at 20° and cooled to −50 to −55°. Hydrocarbon 4 (4.8 g, 0.03 mol) in 5 ml of acetic anhydride was added dropwise over 30 min. The temperature was allowed to rise to 0° and then stirred at 0° for 4 hr. After pouring onto ice and neutralization with solid potassium carbonate, the mixture was extracted

(14) C. D. Hurd and L. H. Juel, *J. Amer. Chem. Soc.*, **77**, 601 (1955).
(15) G. Schroeter, *Chem. Ber.*, **58**, 713 (1925).
(16) S. Julia, M. Julia, and B. Bemont, *Bull. Soc. Chim. Fr.*, 1449 (1959).
(17) J. F. J. Dippy and J. T. Young, *J. Chem. Soc.*, 3919 (1955).
(18) E. LeGoff, *J. Org. Chem.*, **29**, 2048 (1964).

with ether and the extract was washed with water and dried. Removal of ether gave 5.7 g of a yellow oil. Preparative glc on 15% QF-1 (0.375 in. × 50 ft column) gave the desired product, which was further purified by chromatography on neutral alumina with benzene. Removal of solvent gave a solid, mp 96.5–97° (lit.[8] mp 95–96°).

6- and 7-Nitro-4,4-dimethylbenzo[*a*]cyclopropa[*c*]cycloheptene (6′ and 7).—To a solution of 24 ml of acetic anhydride and 8 ml of fuming nitric acid at −40° was added dropwise 5.75 g (0.025 mol) of **6** at a rate such that the temperature did not rise above −20°. The reaction mixture was then allowed to come to room temperature and poured into hot water, the product was extracted with ether, washed with 5% sodium bicarbonate, and dried over magnesium sulfate, and the ether was removed under vacuum. The residue was chromatographed on a silica gel column (60–200 mesh, JTB) (4 × 50 cm) and eluted with a mixture of petroleum ether and ether (80:20) to afford 4 g of pale yellow oil. It was dissolved in petroleum ether and cooled to afford 2 g of pale yellow crystals, mp 66–68°. Recrystallization from petroleum ether gave a product: mp 69.5–71° (**6′**); ir 1345 and 1520 cm^{-1} (NO_2); nmr δ 1.47 (s, 3 H, CH_3), 1.62 (s, 3 H, CH_3), 0.2–2.4 (m, 8 H, aliphatic), 7.6 (d, 1 H, aromatic) and 8.0–8.2 (m, 2 H, aromatic).

Anal. Calcd for $C_{11}H_{17}NO_2$ (**6′**) C, 72.70; H, 7.41; N, 6.06. Found: C, 72.68; H, 7.25; N, 6.32.

The mother liquor was stripped of solvent and rechromatographed on a silica gel column (4 × 50 cm) using hexane to give a pale yellow liquid: $n^{25}D$ 1.5526 (**7**); ir 1515 and 1340 cm^{-1} (NO_2); nmr δ 0.2–2.5 (m, 8 H, aliphatic), 1.41 and 1.60 (s, 3 H, CH_3), 7.9–8.2 (m, 2 H, aromatic), 7.5 (d, 1 H, aromatic).

Anal. Calcd for $C_{11}H_{17}NO_2$ (**7**): C, 72.70; H, 7.41; N, 6.06. Found: C, 72.71; H, 7.37; N, 6.02.

4-Nitro-α-α-dimethylhomophthalic Anhydride (8). A. Authentic.—Potassium nitrate (3.4 g) in 10 ml of concentrated sulfuric acid was added slowly to a solution of 4 g of 3,3-dimethylindanone in 20 ml of concentrated sulfuric acid previously cooled to 0°. The reaction mixture was maintained at 0° for 1 hr and then poured over ice and allowed to stand for 15 min and filtered to give a product, mp 132–133° (lit.[19] mp 131–133°). The nitro ketone (1 g) and 4 g of potassium dichromate were suspended in 20 ml of water and 7 ml of concentrated sulfuric acid was added. After the mixture had cooled to room temperature had been refluxed for 30 min, it was poured over ice and an off-white solid was collected. Crystallization from petroleum ether gave a product, mp 161–163°, ir 1790 and 1750 cm^{-1} (anhydride).

Anal. Calcd for $C_{11}H_9NO_5$: C, 56.18; H, 3.86; N, 5.96. Found: C, 56.37; H, 4.10; N, 5.91.

B. Oxidation of 7.—A solution of 100 mg of **7** and 0.6 g of chromic acid was refluxed for 1 hr, poured into 50 ml of water, and extracted with ether. Removal of solvent afforded a crystalline product, mp 161–162°. Crystallization from acetone gave an off-white crystalline product, mp 162–163°, identical with that described above.

5-Nitro-α,α-dimethylhomophthalic Anhydride (9).—A solution of 200 mg of **6′** and 1 g of chromic acid in 10 ml of acetic acid was refluxed for 1 hr, diluted with 100 ml of water, and extracted with ether. Solvent removal followed by crystallization from petroleum ether afforded off-white crystals, mp 199–200°, ir 1735 and 1750 cm^{-1} (anhydride).

Anal. Calcd: C, 56.18; H, 3.86; N, 5.96. Found: C, 56.40; H, 3.70; N, 5.83.

Registry No.—**1**, 310-53-2; **1′**, 25178-99-8; **2**, 15677-15-3; **2′**, 25178-97-6; **3**, 25033-22-1; **3′**, 25178-98-7; **4**, 25033-23-2; **4′**, 25033-28-7; **6**, 34603-14-0; **6′**, 32113-65-8; **7**, 34603-16-2; **8**, 34603-17-3; **9**, 34603-18-4; PhC_3H_5, 873-49-4; 5,5-dimethyl-6,7-dihydro-5*H*-benzocycloheptene, 34603-19-5; 1,1-dibromo-4,4-dimethylbenzo[*a*]cyclopropa[*c*]cycloheptene, 34603-20-8.

(19) M. K. Goo-On, L. H. Schwatzman, and G. Forrest Woods, *J. Org. Chem.*, **19**, 305 (1954).

Light-Sensitive Glycosides. I. 6-Nitroveratryl β-D-Glucopyranoside and 2-Nitrobenzyl β-D-Glucopyranoside

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Two light-sensitive glucosides, namely, 6-nitroveratryl and 2-nitrobenzyl β-D-glucopyranoside, were prepared and characterized. The two glucosides were more stable to acid hydrolysis, than benzyl β-D-glucopyranoside. They could be photolyzed, however, to give a high yield of D-glucose under conditions that leave the benzyl glucoside intact.

The utilization of light-sensitive blocking groups has great promise in synthetic carbohydrate chemistry and in synthetic chemistry in general. Ideally, such groups should be stable to a wide variety of chemical treatments, on one hand, and at the same time be sensitive to irradiation under conditions that leave other functional groups in the molecule unaffected.

Early studies utilizing photochemical cleavage of blocking groups include the work of Tănăsescu[1] and Heidt.[2] In a series of papers the former investigator used sunlight and long periods of irradiation to remove 2-nitrobenzylidene groupings. The reactions were limited by the fact that (a) not all the 2-nitrobenzylidene groups were affected and (b) di-2-nitrobenzylidene derivatives of different saccharides, namely glucose, mannose, and galactose, were claimed to yield the same galacto derivative following irradiation. The photolysis of different phenyl, benzyl, and phenylethyl glycosides upon irradiation at 254 nm was studied by Heidt.[2] The reported yields, however, were low.

We believe that many of the limitations inherent to the findings of Tănăsescu and Heidt can be overcome by the application of modern irradiation, analytical, and spectroscopic techniques. With the advent of such methods as nmr and ORD the reinvestigation of the stereochemistry of such reactions is especially worthwhile. The results of such a study should place these early contributions in their proper perspective.

Recently, the use of 2-nitrobenzyl derivatives as photosensitive blocking reagents for amino and carboxyl functions in amino acids and peptides has been described.[3–5] In these examples the blocking groups

(1) I. Tănăsescu, *Bull. Soc. Stiiute Cluj*, **2**, 111 (1924); *Chem. Zentr.*, **2**, 2827 (1924); and many later papers including in particular I. Tănăsescu and C. Costache, *Rev. Chim., Acad. Repub. Pop. Roum.*, **1**, 61 (1956).

(2) J. Heidt, *J. Franklin Inst.*, **234**, 473 (1942).

(3) J. A. Barltrop, P. J. Plant, and P. Schofield, *Chem. Commun.*, 882 (1966).

(4) A. Patchornik in "Pharmacology of Hormonal Polypeptides and Proteins," Plenum Press, New York, N. Y., 1968, p 11.

(5) A. Patchornik, B. Amit, and R. B. Woodward, *J. Amer. Chem. Soc.*, **92**, 6333 (1970).

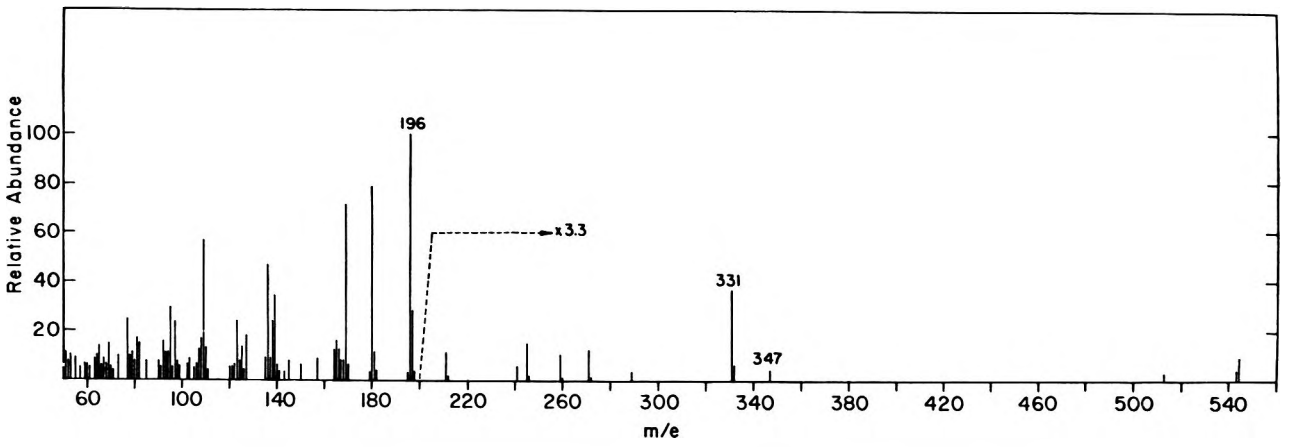


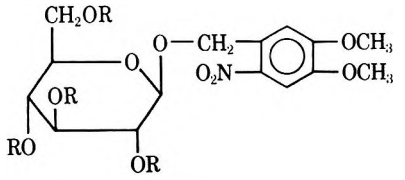
Figure 1.—Mass spectrum of 6-nitroveratryl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**3**).

could be removed in high yields, and it became tempting therefore to try and use them in carbohydrate chemistry where they could be utilized in saccharide modifications and synthesis, in oligosaccharide synthesis, and for a variety of other purposes. One possible example is, for instance, the release of free saccharides in biological systems following a short irradiation.

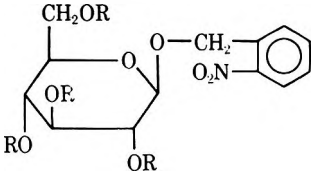
Results and Discussion

6-Nitroveratryl β-D-glucopyranoside (**1**) and 2-nitrobenzyl β-D-glucopyranoside (2) (Scheme I) were

SCHEME I



1, R = H
3, R = $COCH_3$

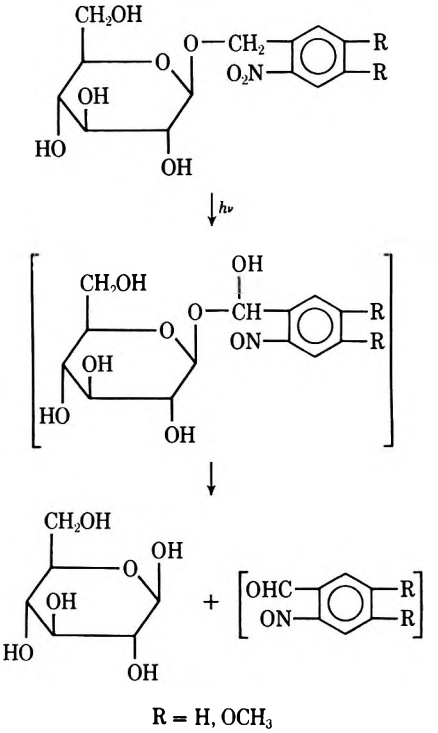


2, R = H
4, R = $COCH_3$

prepared through a modification of the Königs–Knorr reaction employing silver perchlorate in nitromethane. In the course of the reaction side products were formed that complicated the isolation of the desired glucosides. They were isolated conveniently, however, after de-O-acetylation and fractionation on a charcoal or a silica gel column. Both compounds were subjected to acid hydrolysis (0.1 *N* hydrochloric acid, 91°) and compared to benzyl-β-D-glucopyranoside[6] that has a half-life of 590 min under the said conditions (for the hydrolysis of this benzyl glucoside compare also ref 7 and 2). Compounds 1 and 2 hydrolyzed at rates of 0.78 and 0.70, respectively, of that for the benzyl glucoside (1.0). In contrast to their increased stability to acid, compounds 1 and 2, were found to be labile to irradiation at wavelength longer than 320 nm, conditions where the benzyl glucoside remains unaffected. Irradiation of compound 1 yielded 80% hydrolysis after 10 min and quantitative hydrolysis after 30 min. Compound 2 gave under the same conditions quantitative hydrolysis after 10 min. In all cases the hydrolysis was followed by the release of D-glucose, as determined enzymatically with glucose oxidase[8] and was also demonstrated by paper chromatography in two solvent systems as the predominant carbohydrate product, occasionally accompanied by very minute amounts of a faster moving silver nitrate positive spot.

The mechanism of the photochemical reaction (Scheme II) is probably analogous to the one postu-

SCHEME II



R = H, OCH_3

lated[5] involving intramolecular oxidation–reduction, splitting of the newly formed hemiacetal followed by a further condensation of the aromatic moiety.

(6) E. Fischer and B. Helfrich, *Justus Liebigs Ann. Chem.*, **383**, 68 (1911); K. H. Slotta and H. Heller, *Ber.*, **63**, 1024 (1930).
(7) J. Heidt and C. B. Purves, *J. Amer. Chem. Soc.*, **60**, 1206 (1938).
(8) E. Raabo and T. C. Terkildsen, *Scand. J. Clin. Lab. Invest.*, **12**, 402 (1966).

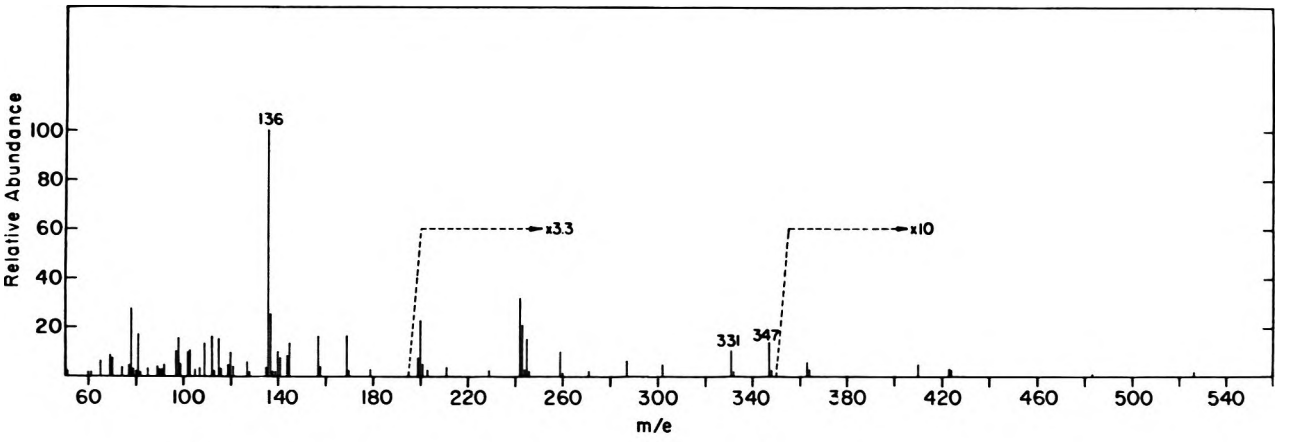


Figure 2.—Mass spectrum of 2-nitrobenzyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (4).

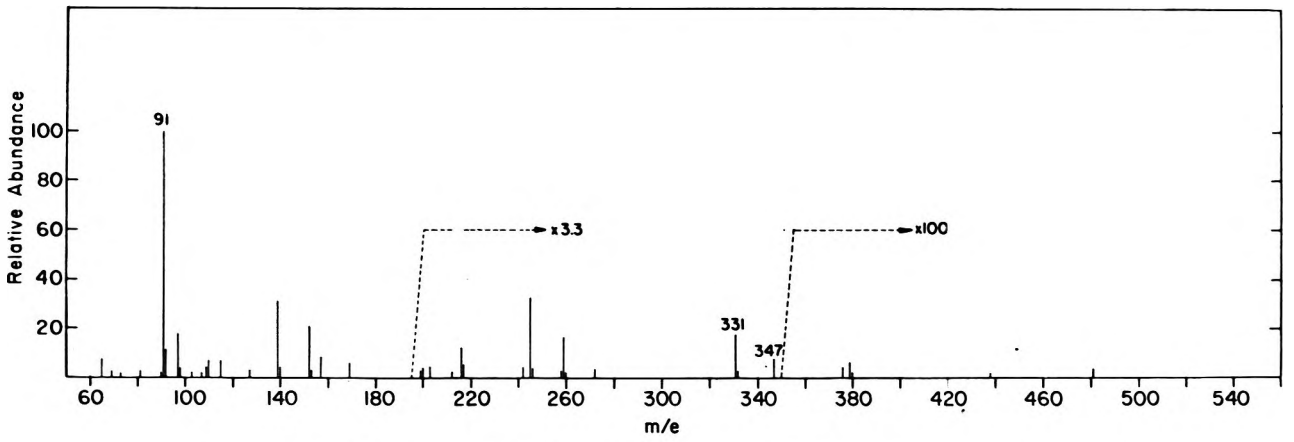
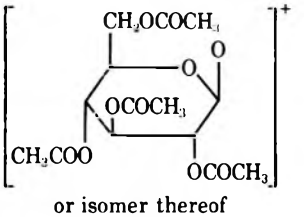


Figure 3.—Mass spectrum of benzyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside.

Acetylation in pyridine of compound **1** and of compound **2** afforded compounds **3** and **4** that served for spectroscopic studies. The infrared spectra were in accord with the proposed structures.

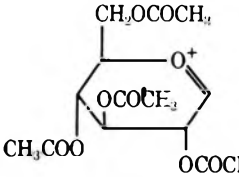
In the mass spectra of the acetylated glucosides (Figures 1–3) one observes in addition to low abundance of molecular ions (*m/e* 543, 483, and 438, respectively) in two cases (Figures 2 and 3) ions corresponding to M + 43.[9] Three major primary fragmentation processes are present leading to the formation of M-substituted benzyl radical (*m/e* 347), M-substituted benzyloxy radical (*m/e* 331), and the substituted benzyl (or tropylium) ion (Scheme III). The ratio of the intensities of the peaks at *m/e* 347 and 331 is different for the different glucosides. The extent of their further fragmentation through the loss of acetic acid and ketene (60 and 42 mass units, respectively) is also different for the three glucosides. The effect of substitution in the aglycone is manifested not only in the first stage of fragmentation but also in the decomposition of resulting ions of identical composition and which do not contain the substituted aglycone any more. This effect might be explained by the assumption that the ions *m/e* 347 and 331 are produced in the different cases with different internal energy distributions dependent on the substituents. The last phenomenon has been described for a few simpler cases.[10]

SCHEME III

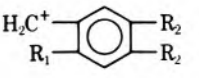


or isomer thereof

m/e 347



m/e 331



m/e 196; $R_1 = NO_2$, $R_2 = OCH_3$ (Fig. 1)
m/e 136; $R_1 = NO_2$, $R_2 = H$ (Fig. 2)
m/e 91; $R_1 = R_2 = H$ (Fig. 3)

It is pertinent to note that the photochemical removal of *O*-nitrobenzyl blocking groups under the conditions described here occurs at high yield, which is a prerequisite for their utilization in synthetic organic chemistry where the blocking groups can be removed following a sequence of synthetic steps. One should

(9) J. H. Beynon, "Mass Spectrometry and Its Application to Organic Chemistry," Elsevier, Amsterdam, 1960, p 276; H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. 2, Holden-Day, San Francisco, Calif., 1964, p 217.

(10) F. W. McLafferty and M. L. Gross, *Chem. Commun.*, 254 (1968); R. H. Shapiro, J. Turk, and J. W. Serum, *Org. Mass Spectrom.*, **3**, 171 (1970); S. Kozuda, H. Takahashi, S. Tamagaki, and S. Oae, *Bull. Chem. Soc. Jap.*, **43**, 1408 (1970).

also note that, in distinction from previous reports, no degradation[2] or change of configuration[1] in the carbohydrate moiety occurs in our case as the result of the photochemical reaction.

Experimental Section

All melting points are corrected. Optical rotations were determined with a Bendix polarimeter. The ir spectra were measured with a Perkin-Elmer Model 237 spectrophotometer in chloroform or in KBr disks. Nmr spectra were recorded on a Varian A-60 or a Brockmann HFX-10 instrument with tetramethylsilane as an internal standard; unless otherwise mentioned, exchangeable protons are not listed. The uv spectra were taken on a Cary Model 14 spectrophotometer and colorimetric determinations were done on a Klett-Summerson colorimeter equipped with filter no. 50. Mass spectra were measured on an Atlas CH4 mass spectrometer with 70 eV ionizing current. The samples were introduced through a direct inlet system and heating was applied until the vapor pressure was sufficient to obtain useable mass spectra. Acetyl (*m/e* 43) was always the most abundant peak. Column chromatography was carried out on Silica Gel "Grace," Davison Chemical Corp., grade 950, 60–200 mesh. Thin layer chromatography was carried out and the spots were observed under a uv lamp on fluorescent silica gel plates DF-B, Camag, Muttenz, Switzerland. R_{SR} refers to mobility relative to sudan red, a component of the test mixture supplied by C. Desaga, Heidelberg, Germany.

Paper chromatography was performed on Whatman No. 1 paper. The paper was developed with descending *n*-butyl alcohol–acetic acid–water (25:6:25, v/v/v, upper phase) I or with descending ethyl acetate–pyridine–water (2:1:2, v/v/v, upper phase) II. The chromatograms were revealed by silver nitrate[11] and by glucose oxidase spray.[12] Thick layer chromatography was done on "Chromar 1000" sheets supplied by Mallinckrodt. Sheets (20 × 20 cm) were developed with chloroform and viewed under a uv lamp. The band of the desired material was extracted with chloroform, filtered, and evaporated. 2-Nitrobenzyl alcohol was purchased from Fluka, Switzerland.

6-Nitroveratryl Alcohol.—6-Nitroveratraldehyde[13] (1.05 g, 5 mmol) was dissolved in a mixture of dioxane (10 ml) and methanol (15 ml). Sodium borohydride (0.57 g) was added and the mixture was stirred for 15 min at room temperature. The solvents were then evaporated *in vacuo* from the reaction mixture, water (50 ml) was added, and the suspension was stirred for an additional 5 min. The solid was collected after filtration, dried over phosphorus pentoxide, and crystallized from ethanol, yield 0.85 g (80%), mp 142°.

Anal. Calcd: C, 50.70; H, 5.20; N, 6.52. Found: C, 50.52; H, 5.03; N, 6.70.

6-Nitroveratryl β-D-Glucopyranoside (1).—A mixture of bromo-2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside ("acetobromoglucose")[14] (2.05 g, 5.0 mmol), 6-nitroveratryl alcohol (1.1 g, 5.2 mmol), calcium sulfate (200 mg), and calcium carbonate (500 mg) in anhydrous nitromethane (10 ml) was stirred under a calcium chloride seal at −16° for 30 min. Anhydrous silver perchlorate (1.0 g) was added and the stirring was continued for 1 hr at −16° and overnight at room temperature. The mixture was filtered through a Celite filter with the aid of some ethyl acetate and evaporated. The oily residue was dissolved in a methanolic solution of barium methoxide (0.1 *M*, 25 ml) and was left overnight at room temperature. The solution was then neutralized with carbon dioxide, evaporated *in vacuo*, and extracted with 25% ethanol (5 ml), and the resulting solution was applied to a charcoal column (Darco G 60, Celite 535, 1:1; 80 cm long, 1.0 cm diameter). The column was first washed with a gradient of water (500 ml) and 50% ethanol (500 ml). Compound 1 (amorphous yellow solid, 300 mg, 16%) was eluted subsequently as a broad, homogeneous peak (uniform by tlc, phenol–sulfuric acid test[15] on 1-ml samples and optical rotation throughout the peak) with another gradient of 50% ethanol (500 ml) and 70% ethanol (500 ml). The product was recrystallized from methanol–ethyl acetate: mp 172–175°; $[\alpha]^{23}D$ −1.7 ± 0.5° (*c* 0.7, pyridine); R_{SR} 0.70 (acetone–methanol, 3:1), R_{SR} 0.0 (chloroform).

Anal. Calcd for $C_{17}H_{29}O_{12}N$ ($C_{15}H_{21}O_{10}N \cdot 2CH_4O$): C, 46.45; H, 6.66; N, 3.18. Found: C, 46.26; H, 5.99; N, 3.39.

Compound 1 could also be crystallized from water: mp 186°; $[\alpha]^{25}D$ −5.0 ± 0.5° (*c* 1.6, pyridine); uv max (water) 348 nm (ε 6.1 × 10²), 304 (5.0 × 10²), 242 (1.0 × 10³); nmr (90 MHz, dimethyl sulfoxide-d_6, hexamethylsiloxane as an external standard) τ 2.08 and 2.10 (apparent d, 2, aromatic), 4.75 (s, 2, benzylic CH_2), 5.48 (d, 1, H-1, $J_{1,2}$ = 7.0 Hz), 5.92 (s, 3, OCH_3), 5.98 (s, 3, OCH_3), 6–7 (ring protons and C-5 CH_2).

Anal. Calcd for $C_{15}H_{21}O_{10}N$: C, 48.00; H, 5.64; N, 3.73. Found: C, 47.77; H, 5.53; N, 3.75.

2-Nitrobenzyl β-D-Glucopyranoside (2).—The preparation described for compound 1 was repeated with 2-nitrobenzyl alcohol (0.79 g, 5.2 mmol) instead of with 6-nitroveratryl alcohol. Following the neutralization with carbon dioxide the solution was evaporated *in vacuo* and extracted with methanol and the resulting solution was evaporated on silica gel (10 g). The absorbed material was placed on top of a silica gel column (100 g, 2 cm diameter) packed in ethyl acetate. The column was first washed with ethyl acetate (400 ml) and 5% acetone in ethyl acetate (400 ml). Compound 2 was then eluted as a broad, homogeneous peak (by tlc) with 10, 20, 30, and 50% acetone in ethyl acetate (400 ml each), yield 1.1 g (69%). The product was crystallized from water as yellow prisms that sintered at 90–95°: mp 131°; $[\alpha]^{25}D$ −4.39 ± 0.5° (*c* 0.55, pyridine); R_{SR} 0.68 (acetone–methanol, 3:1); uv max (water) 265 nm (ε 5.4 × 10³).

Anal. Calcd for $C_{13}H_{19}O_9N$ ($C_{13}H_{17}O_8N \cdot H_2O$): C, 46.84; H, 5.74; N, 4.20. Found: C, 46.77; H, 5.54; N, 4.20.

A sample of compound 2 was dried at 80° under high vacuum for 5 hr, yielding opaque crystals, mp 126°.

Anal. Calcd for $C_{13}H_{17}O_8N$: C, 49.52; H, 5.44; N, 4.44. Found: C, 49.36; H, 5.43; N, 4.28.

6-Nitroveratryl 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranoside (3).—Compound 1 (90 mg) was dissolved in dry pyridine (3.0 ml), acetic anhydride (1.0 ml) was added, and the mixture was left overnight at room temperature. A crystal of ice was then added and after 1 hr the solution was evaporated *in vacuo* with the aid of some benzene. The yellow oily residue that solidified after prolonged storage, (103 mg, 86%) was almost pure by tlc, R_{SR} 0.60 (chloroform), and was further purified on two sheets of "Chromar 1000:" $[\alpha]^{23}D$ −3.81 ± 0.5° (*c* 0.7, chloroform); nmr (60 MHz, $CDCl_3$) τ 2.15 (s, 2, aromatic), 4.3–5.9 (m, 9), 4.63 (s, benzylic CH_2), 5.93 (s, 3, OCH_3), 5.97 (s, 3, OCH_3), 7.88 (s, 3, $OCOCH_3$), 7.94 (s, 9, three $OCOCH_3$).

Anal. Calcd for $C_{23}H_{29}O_{14}N$: C, 50.83; H, 5.38. Found: C, 50.14; H, 5.25.

2-Nitrobenzyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (4) was prepared by acetylation of compound 2 as described for the preparation of compound 3: yield, after chromatography, 75 mg (57%) of yellow, glassy residue that solidifies; R_{SR} 0.54 (chloroform); $[\alpha]^{25}D$ −7.5 ± 0.5° (*c* 2.0, chloroform); nmr (60 MHz, $CDCl_3$) τ 1.8–2.5 (m, 4, aromatic), 4.5–6.4 (m, 9), 4.86 (apparent d, benzylic CH_2, *J* = 5.0 Hz), 7.93 (s, 3, $OCOCH_3$), 7.95 (s, 3, $OCOCH_3$).

Anal. Calcd for $C_{21}H_{25}O_{12}N$: C, 52.17; H, 5.21. Found: C, 51.87; H, 5.07.

Acid Hydrolysis.—Samples (1.0 ml, 0.555 m*M* in 0.1 *N* hydrochloric acid) of benzyl β-D-glucopyranoside, compound 1, and compound 2 in closed ampoules were kept at 91° for different periods of time (0–20 hr). The ampoules were subsequently stored at 4° until analyzed for their glucose content. Samples after 20 hr of hydrolysis were also lyophilized, dissolved in water (50 μl), and checked (20 μl) by paper chromatography in systems I and II. The chromatograms were stained with silver nitrate or with glucose oxidase spray reagent.

Photolysis.—Samples (1.0 ml, 0.555 m*M* in water or in 1/15 *M* potassium dihydrogen phosphate, disodium hydrogen phosphate buffer, pH 7.0) of benzyl β-D-glucopyranoside, compound 1, and compound 2 in Pyrex test tubes that had been evacuated and closed were irradiated in a RPR-100 apparatus (Rayonet, the Southern Co., Middletown, Conn.) with 320-nm lamps. The tubes were kept in the dark until analyzed for their glucose con-

(11) N. Sharon and R. W. Jeanloz, *J. Biol. Chem.*, **235**, 1 (1960).

(12) M. R. J. Salton, *Nature (London)*, **186**, 966 (1960); A. Martinsson, *J. Chromatogr.*, **24**, 487 (1966).

(13) C. A. Fetscher, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 735.

(14) C. E. Redemann and C. Niemann, *Org. Syn.*, **22**, 1 (1942).

(15) M. Dubois, K. A. Gilles, J. K. Hamilton, P. A. Rebers, and F. Smith, *Anal. Chem.*, **28**, 350 (1956).

tent. Samples after 4 hr irradiation were also lyophilized and checked by paper chromatography as described above.

Registry No.—**1**, 34546-52-6; **2**, 34546-53-7; **3**, 34546-54-8; **4**, 34546-55-9; 6-nitroveratryl alcohol, 1016-58-6.

Acknowledgments.—We wish to thank Dr. Asher Mandelbaum for his help in the interpretation of mass spectra. This work was supported by Grant No. AM05098 from the National Institutes of Health, Public Health Service.

Light-Sensitive Glycosides. II. 2-Nitrobenzyl 6-Deoxy-α-L-mannopyranoside and 2-Nitrobenzyl 6-Deoxy-β-L-galactopyranoside

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Received October 26, 1971

The two title compounds possessing α and β anomeric structures were prepared, characterized, and photochemically split to 6-deoxymannose (rhamnose) and 6-deoxygalactose (fucose), respectively. 2-Nitrobenzyl 6-deoxy-2,3-isopropylidene-α-L-mannopyranoside was synthesized and the isopropylidene grouping subsequently removed by acid hydrolysis without affecting the nitrobenzyl glycoside.

In the preceding paper[1] we have described a 6-nitroveratryl and a 2-nitrobenzyl β-D-glucopyranoside. Both compounds were found to be more stable to acid hydrolysis than benzyl β-D-glucopyranoside and were susceptible to photolysis under conditions that do not affect the benzyl glucoside.

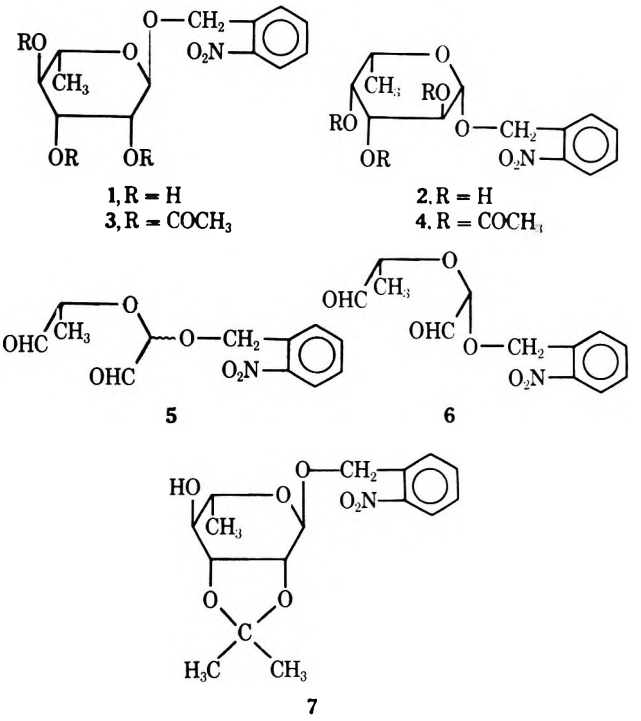
In the present work we tried to broaden the scope of our investigation to glycosides of different configurations and different anomeric structure. We also prepared and hydrolyzed an isopropylidene derivative without affecting the glycoside. Such an isopropylidene derivative might serve as a convenient intermediate in carbohydrate synthesis.

Results and Discussion

2-Nitrobenzyl 6-deoxy-α-L-mannopyranoside (**1**) and 2-nitrobenzyl 6-deoxy-β-L-galactopyranoside (**2**) were prepared by the Zémplen modification[2] of the Königs–Knorr reaction, followed by de-O-acetylation with barium methoxide and fractionation on silica gel. Compound **2** was accompanied by what is, most probably, the α anomer. The Zémplen modification was chosen as it was reported to yield clean 6-deoxy-α-mannopyranosides.[3] The optical rotations, uv, ir, and nmr spectra of the two compounds and their acetates (**3** and **4**) were in accord with the proposed structures (Scheme I). Only in the case of compound **4** (and hence compound **2**), however, had the anomeric configuration firm support from the nmr data, $J_{1,2}$ = 7.5 Hz, that should correspond to *axial–axial* interaction present in the β anomer. The anomeric configuration in compound **1** was established by its periodate oxidation to the dialdehyde **5** possessing a different rotation from the corresponding dialdehyde **6** obtained in a similar oxidation of compound **2**. As a result, compound **1** was assigned as the α anomer.

Irradiation of compounds **1** and **2** afforded quantitatively 6-deoxymannose (rhamnose) and 6-deoxygalactose (fucose), respectively, as determined by viewing the chromatograms. The reducing sugar tests gave too high yields (over 120%) due to the interference of the formed aldehyde. In the preceding work this difficulty was overcome by the enzymic determination of D-glucose that was formed during the cleavage.

SCHEME I



The isopropylidene derivative (**7**) of compound **1** was prepared in high yield, using copper sulfate in acetone. The material absorbed at 3620 and 3480 cm^{-1} (OH) indicative of a free hydroxy grouping. Such a group on C-4 should be available for selective chemical modification. In view of the increased stability of the 2-nitrobenzyl glycosides to acid hydrolysis, the isopropylidene moiety could be neatly removed by sulfuric acid in aqueous acetone (Figure 1) without affecting the glycoside function.

The mass spectra of compounds **3** and **4** (Figures 2 and 3) are in principle similar to the spectra of the glucosides described before.[1] The molecular ions, however, are absent and one observed four major primary fragments: M − acetic acid, *m/e* 365; M − nitrobenzyl radical, *m/e* 289; M − nitrobenzyloxy

(1) Part I: U. Zehavi, B. Amit, and A. Patchornik, *J. Org. Chem.*, **37**, 2281 (1972).
(2) G. Zémplen, *Ber.*, **62**, 990 (1929).
(3) P. A. J. Gorin and A. S. Perlin, *Can. J. Chem.*, **37**, 1930 (1959).

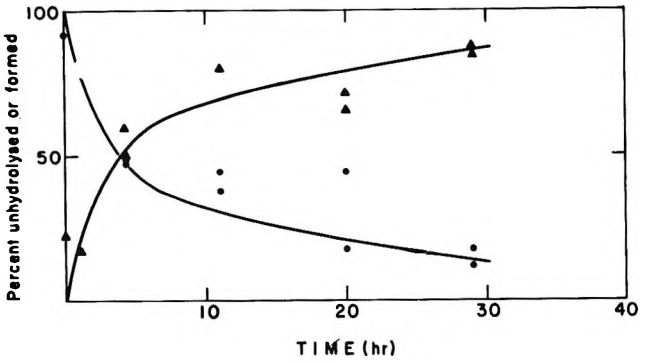


Figure 1.—Acid hydrolysis of compound **7** (●) and formation of compound **1** (▲). For details see Experimental Section.

ferent for the two cases as a result of the difference in configuration and anomeric structure of compounds **3** and **4**.

A pronounced difference between compounds **3** and **4** can be found in the fragmentation patterns of compound **3**, starting probably from *m/e* 289 to give an intense line line at *m/e* 244 (loss of HCO_2). Subsequently a loss of acetic acid results in an ion of *m/e* 184. A less important fragmentation of the same compound is through the formation of *m/e* 229 (a possibility of *m/e* 289 losing acetic acid) and *m/e* 184 (loss of HCO_2). A metastable peak is present only for the transition of *m/e* 244 to *m/e* 184. Only the second pattern is present in the spectrum of compound **4**. It is of interest to

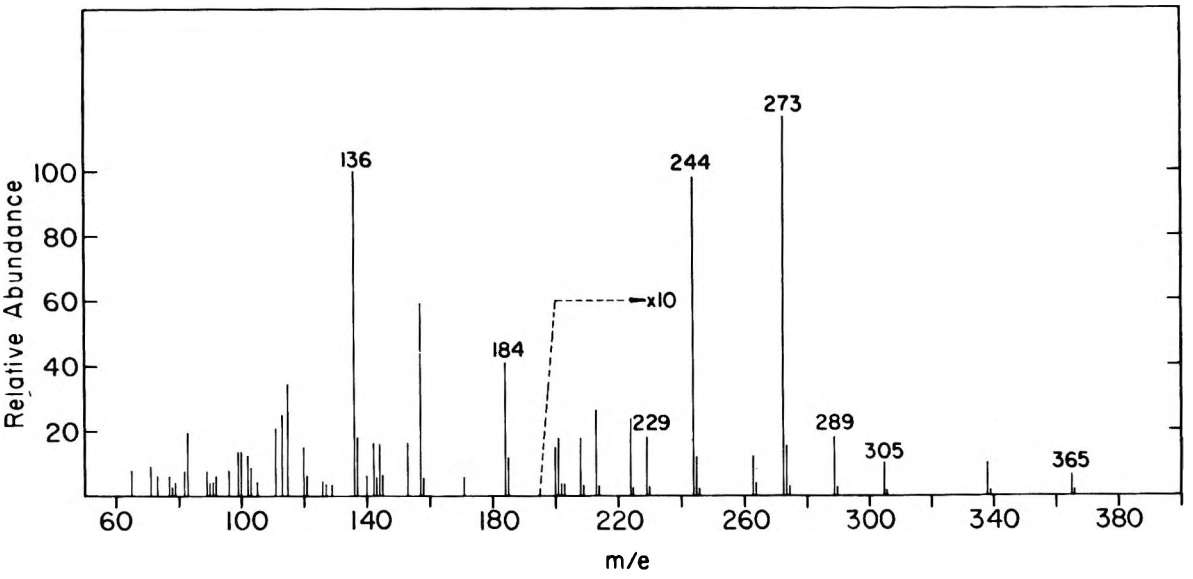


Figure 2.—Mass spectrum of 2-nitrobenzyl 6-deoxy-2,3,4-tri-*O*-acetyl-α-L-mannopyranoside (**3**).

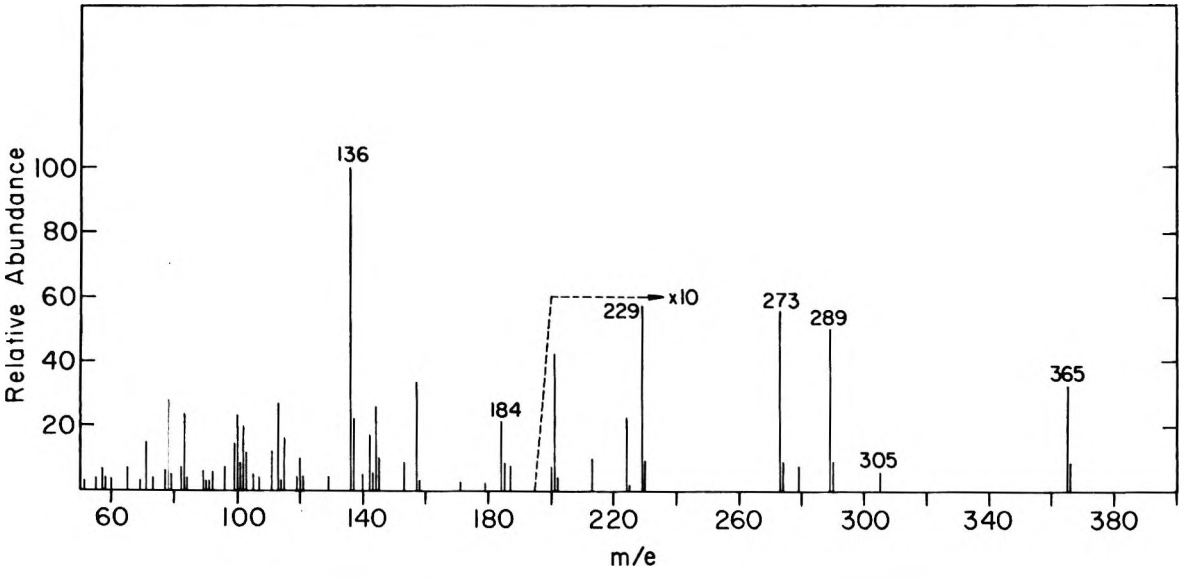
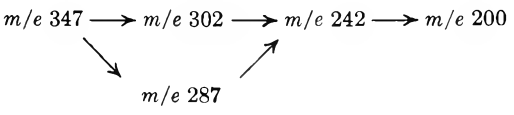


Figure 3.—Mass spectrum of 2-nitrobenzyl 6-deoxy-2,3,4-tri-*O*-acetyl-β-L-galactopyranoside (**4**).

radical, *m/e* 273; and nitrobenzyl (or an isomeric form) ion, *m/e* 136. The first three ions are further decomposed through the loss of acetic acid and ketene (60 and 42 mass units, respectively). The relative abundances of the parent fragments as well as the abundance of products of further degradation, occurring through the loss of 60 and 42 mass units, are different for the two cases as a result of the difference in configuration and anomeric structure of compounds **3** and **4**.

A pronounced difference between compounds **3** and **4** can be found in the fragmentation patterns of compound **3**, starting probably from *m/e* 289 to give an intense line line at *m/e* 244 (loss of HCO_2). Subsequently a loss of acetic acid results in an ion of *m/e* 184. A less important fragmentation of the same compound is through the formation of *m/e* 229 (a possibility of *m/e* 289 losing acetic acid) and *m/e* 184 (loss of HCO_2). A metastable peak is present only for the transition of *m/e* 244 to *m/e* 184. Only the second pattern is present in the spectrum of compound **4**. It is of interest to note that both patterns are present in the spectrum of 2-nitrobenzyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside,[1]



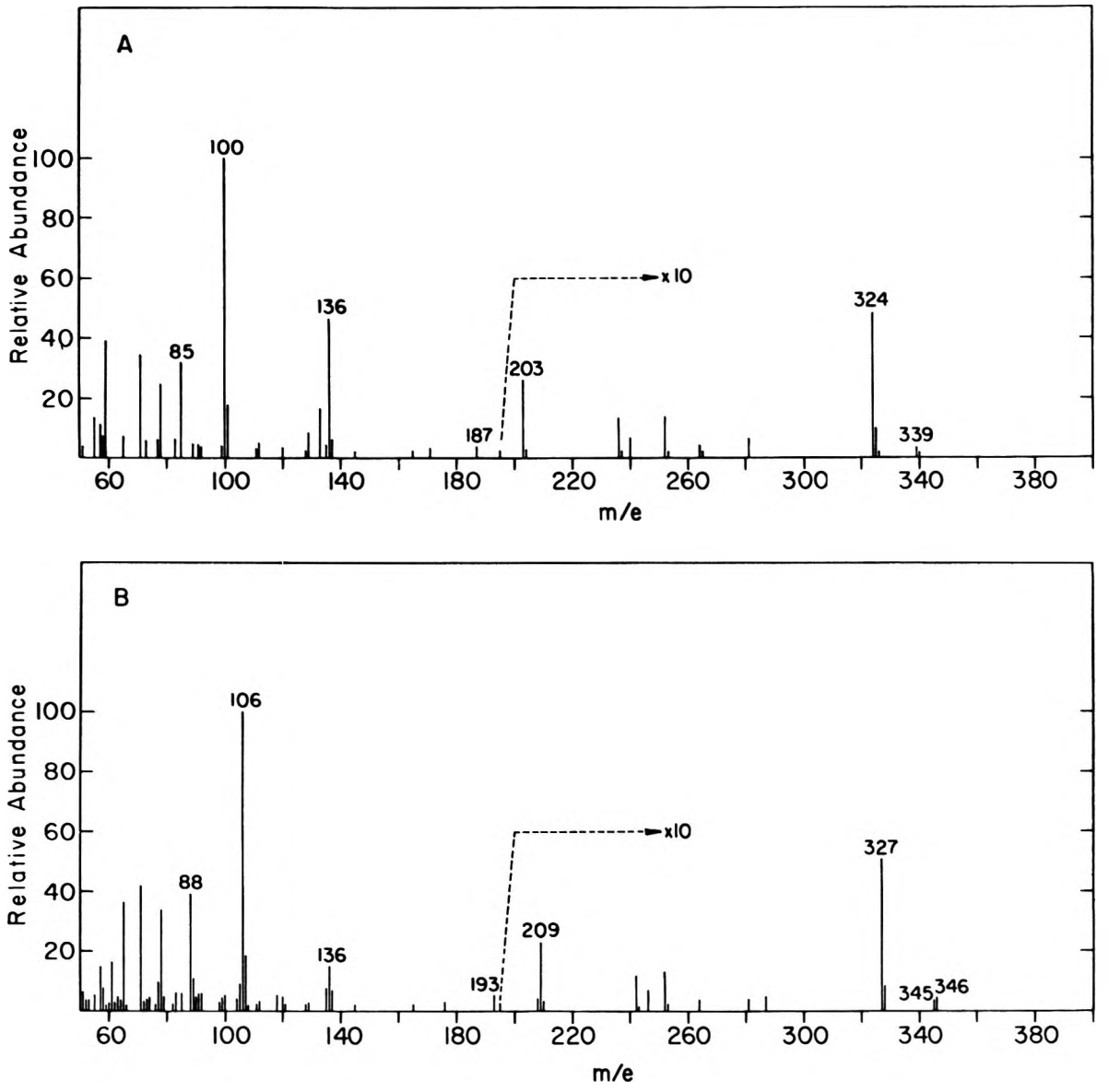


Figure 4.—Mass spectra of (A) 2-nitrobenzyl 6-deoxy-2,3-isopropylidene-α-L-mannopyranoside (7); (B) 2-nitrobenzyl 6-deoxy-2,3-(isopropylidene-d_6)-α-L-mannopyranoside.

and metastable peaks are present for transitions other than the loss of 45 mass units. The two patterns are absent from the spectrum of 6-nitroveratryl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside and present to a small extent in that of benzyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside.[1]

In the mass spectra of compound **7** and its isopropylidene-d_6 derivative (mass units indicated in brackets) (Figure 4) one can easily interpret the following peaks: the molecular peak M, 339 (345); M + 1, 340 (346); M − CH_3 from isopropylidene, 324 (327); M − nitrobenzyl, 203 (209); M − nitrobenzyloxy, 187 (193); nitrobenzyl, 136 (136); nitrosobenzyl, 120 (120), 100 (106), and 85 (88), with a metastable peak at *m/e* 72.3 suggesting the following structures for the last two peaks (Scheme II).

In the present work we have demonstrated that light-sensitive α- and β-glycosides of saccharides other than glucose can be conveniently prepared and derivatized. The glycosides were photolyzed in high yield to the parent sugars.

SCHEME II

m/e 100 *m/e* 85

Experimental Section

Experimental procedures were the same as those reported in the preceding paper.[1] Nmr spectra were also recorded on a Varian HA-100 instrument and colorimetric determinations were done on a Zeiss Model PMQ II spectrometer.

Paper chromatograms were revealed by silver nitrate.[4] Thick layer chromatography was done on "Chromar-1000" sheets, supplied by Mallinckrodt, 20 × 20 cm sheets were developed with ether–hexane (1:1) and viewed under a uv lamp, and the band of the desired material was extracted with chloroform, filtered, and evaporated. 6-Deoxy-L-mannose (L-rhamnose) and 6-deoxy-L-galactose (L-fucose) were purchased from Pfanstiehl Laboratories, Waukegan, Ill. 2-Nitrobenzyl alcohol was a product of Fluka, Switzerland.

(4) N. Sharon and E. W. Jeanloz, *J. Biol. Chem.*, **235**, 1 (1960).

2-Nitrobenzyl 6-Deoxy-α-L-mannopyranoside (1). A.—A mixture of bromo-6-deoxy-2,3,4-tri-*O*-acetyl-α-L-mannopyranoside ("acetobromorhamnose")[5] (2.1 g, 6.0 mmol), mercuric acetate (0.9 g), 2-nitrobenzyl alcohol (0.91 g, 6.0 mmol), and anhydrous calcium sulfate (1 g) in absolute benzene (30 ml) under a calcium chloride seal was stirred for 20 min inside a 50° bath and for 3 days at room temperature. The mixture was filtered through a Celite filter with the aid of some benzene. The benzene solution was washed with water, dried over calcium chloride, and evaporated *in vacuo* and the residue was left overnight in a methanolic solution of barium methoxide (0.1 *M*, 25 ml). The solution was then neutralized with carbon dioxide, evaporated *in vacuo*, and extracted with methanol, and the resulting solution was evaporated on silica gel (10 g). The absorbed material was placed on top of a silica gel column (100 g, 2 cm diameter) packed in ethyl acetate. The column was washed with ethyl acetate (400 ml) and 10% acetone in ethyl acetate and the product was then eluted with an additional amount of the same solvent (500 ml). The product was homogeneous by tlc, R_{SR} 0.83 (acetone–methanol, 3:1), R_{SR} 0.32 (acetone–ethyl acetate, 1:1). It was crystallized from water to give 508 mg (28%) of elongated yellow-brown plates: mp 103°; $[\alpha]^{24}D$ −18.3 ± 0.3° (*c* 0.9, ethanol); uv max (ethanol) 257 nm (ε 5.6 × 10³); nmr (60 MHz, dimethyl sulfoxide-d_6) τ 1.8–2.4 (m, 4, aromatic), 5.13 (apparent d, benzylic CH_2, J = 2.0 Hz), 8.87 (d, 3, C-5 CH_3, $J_{5,6}$ = 5.5 Hz).

Anal. Calcd for $C_{13}H_{17}O_7N \cdot {}^1/_2H_2O$: C, 50.69; H, 5.88; N, 4.54. Found: C, 50.60; H, 5.88; N, 4.50.

The crystals lost water upon drying at 95° for 3 hr and under high vacuum, mp 110–112°.

Anal. Calcd for $C_{13}H_{17}O_7N$: C, 52.17; H, 5.73. Found: C, 52.20; H, 5.75.

B.—Compound **7** (0.2%) in a mixture of acetone and aqueous 1% sulfuric acid (2:1) was kept at room temperature (23°) and samples (10 μl) were applied for tlc (ethyl acetate–acetone, 1:1) after different time intervals. The plates were viewed under uv and the spots corresponding to compounds **1** and **7** were extracted with ethanol (2.0 ml), filtered through a cotton plug, and read at 257 nm. No 2-nitrobenzyl alcohol, R_{SR} 0.70 (ether–hexane, 1:1), could be observed following 50 hr of hydrolysis. Compound **7** had R_{SR} 0.30 and compound **1** R_{SR} 0.0 in the last solvent system.

2-Nitrobenzyl 6-Deoxy-β-L-galactopyranoside (2).—This compound was prepared as described for compound **1** but with amounts increased tenfold and starting from bromo-6-deoxy-2,3,4-tri-*O*-acetyl-L-galactopyranoside ("acetobromofucose").[6] Following de-O-acetylation the mixture was absorbed on silica gel (50 g) and placed on top of a silica gel column (350 g). The column was first washed with ethyl acetate (1200 ml) and 5% acetone in ethyl acetate (350 ml). An impure oily product (0.37 g) that appears to be the α anomer, R_{SR} 0.60 (ethyl acetate–acetone, 1:1), emerged on further elution with the same solvent (500 ml). The last material was eluted together with increasing amounts of compound **2**, R_{SR} 0.26 (ethyl acetate–acetone, 1:1) (1.0 g), in the next fractions of 10% acetone in ethyl acetate (500 ml) while chromatographically pure compound **2** was eluted subsequently by 25% acetone in ethyl acetate (500 ml) (1.3 g, 7%). It was crystallized from a mixture of methanol and water (but has high solubility in this mixture). The yellow crystals sinter at 46–48° and melt at 136°: $[\alpha]^{24}D$ +4.4 ± 0.5° (*c* 0.69, ethanol); uv max (ethanol) 257 nm (ε 5.8 × 10²); nmr (60 MHz, dimethyl sulfoxide-d_6) τ 1.8–2.6 (m, 4, aromatic), 4.47 (apparent d, 2, benzylic CH_2, J = 2.0 Hz), 8.86 (d, 3, C-5 CH_3, $J_{5,6}$ = 6.0 Hz).

Anal. Calcd for $C_{13}H_{17}O_7N \cdot 1^1/_2 H_2O$: C, 47.88; H, 6.18; N, 4.29. Found: C, 48.13; H, 6.10; N, 4.32.

The water of crystallization could be removed by drying the crystals at 75° for 4 hr and under high vacuum, mp 136°.

Anal. Calcd for $C_{13}H_{17}O_7N$: C, 52.17; H, 5.73. Found: C, 52.39; H, 5.60.

2-Nitrobenzyl 6-Deoxy-2,3,4-tri-*O*-acetyl-α-L-mannopyranoside (3).—Compound **1** (100 mg) was dissolved in pyridine (1.0 ml), and acetic anhydride (0.5 ml) was added. The reaction mixture was left overnight at room temperature, a crystal of ice was then added, and the mixture was left for an additional 2 hr. It was then evaporated *in vacuo* by codistillation with benzene and the product was purified by thick layer chromatography on two sheets: yield 102 mg (79%) of yellow oil; R_{SR} 0.52 (ether–hexane, 1:1), $[\alpha]^{23}D$ −22.7 ± 0.1 (*c* 4.0, chloroform); nmr (100 MHz, $CDCl_3$) τ 1.8–2.6 (m, 4, aromatic), 4.5–5.2 (unresolved m, 6, CH_2, H-1, H-2, H-3, H-4), 6.04 (octet, 1, H-5, $J_{4,5}$ = 9.5, $J_{5,6}$ = 6.0 Hz), 7.81 (s, 3, $OCOCH_3$), 7.92 (s, 3, $OCOCH_3$), 7.94 (s, 3, $OCOCH_3$), 8.72 (d, C-5 CH_3). Irradiation at τ 8.72 caused the collapse of the octet at τ 6.04 to a doublet (J = 9.5 Hz). Irradiation at τ 6.04 caused the collapse of the doublet at τ 8.72 to a singlet; the multiplet τ 4.5–5.2 was also affected.

Anal. Calcd for $C_{15}H_{23}O_{10}N$: C, 53.64; H, 5.54. Found: C, 53.54; H, 5.64.

2-Nitrobenzyl 6-deoxy-2,3,4-tri-*O*-acetyl-β-L-galactopyranoside (4) was prepared as described for compound **3** but starting from compound **2**: yield 103 mg (79%) of yellow oil; R_{SR} 0.41 (ether–hexane, 1:1); $[\alpha]^{23}D$ −19.4 ± 0.2° (*c* 1.0, chloroform); nmr (90 MHz, $CDCl_3$) τ 1.80–2.67 (m, 4, aromatic), 4.58–5.13 (m, 5, CH_2, H-2, H-3, H-4), 5.39 (d, 1, H-1, $J_{1,2}$ = 7.5 Hz), 6.14 (apparent q, 1, H-5, $J_{4,5}$ = 1.5, $J_{5,6}$ = 6.5 Hz), 7.81 (s, 3, $OCOCH_3$), 7.96 (s, 3, $OCOCH_3$), 8.01 (s, 3, $OCOCH_3$), 8.74 (d, 3, C-5 CH_3). Irradiation at 334 Hz (H-5) causes the collapse of the τ 8.74 doublet to a singlet.

Anal. Calcd for $C_{19}H_{23}O_{10}N$: N, 3.29. Found: N, 3.25.

Photolysis of Compounds 1 and 2.—Samples (2.3 × 10^{-2} m*M* in 10% ethanol) were irradiated for 5 hr in closed Pyrex test tubes and then analyzed for their saccharide content by the Park-Johnson color test for reducing sugars[7] using 6-deoxy-L-mannose and 6-deoxy-L-galactose standards.

For the purpose of paper (systems I and II) and thin layer chromatography (ethyl acetate–acetone) 1.0 m*M* solutions in 50% ethanol were irradiated for the same length of time.

The photochemical reactions were carried out in a RPR-100 apparatus (Rayonet, the Southern Co., Middletown, Conn.) with 320-nm lamps.

Periodate Oxidation of Compounds 1 and 2.[8]—Sodium metaperiodate (0.6 ml, 100 mg/ml in water) was added to samples of compound **1** (2.67 mg in 0.3 ml of ethanol) and of compound **2** (2.06 mg in 0.3 ml of ethanol) and the solutions were stored in the dark at room temperature. The optical rotation of the solutions was followed and did not change between 4 and 16 hr. The conversion to the dialdehydes **5** and **6**, respectively (mol wt 255), was then assumed to be quantitative. Dialdehyde **5** had $[\alpha]^{25}D$ −96° and dialdehyde **6** had $[\alpha]^{25}D$ +57°.

2-Nitrobenzyl 6-Deoxy-2,3-isopropylidene-α-L-mannopyranoside (7).—Compound **1** (300 mg) and anhydrous copper sulfate (3 g) were stirred vigorously in acetone (50 ml) overnight at room temperature. According to tlc already after 8 hr most of the starting material was transformed into the isopropylidene derivative **7**, R_{SR} 1.0 (ethyl acetate–acetone, 1:1). The mixture was filtered through a Celite pad with the aid of some additional acetone and the solution was evaporated *in vacuo*, yielding 353 mg of practically pure oil that was further purified by thick layer chromatography on two sheets. The product, 260 mg (79%), was a yellow oil: $[\alpha]^{25}D$ −17.5 ± 0.2° (*c* 1.56, chloroform); uv max (chloroform) 257 nm (ε 6.5 × 10³); nmr (60 MHz, $CDCl_3$) τ 1.8–2.6 (m, 4, aromatic), 4.92 (apparent d, benzylic CH_2, J = 3.5 Hz), 8.46 and 8.63 (two s, 6, isopropylidene), 8.70 (d, 3, C-5 CH_3, $J_{5,6}$ = 6.5 Hz).

Anal. Calcd for $C_{16}H_{21}O_7N$: N, 4.13. Found: N, 4.00.

2-Nitrobenzyl 6-deoxy-2,3-(isopropylidene-d_6)-α-L-mannopyranoside was prepared in an analogous manner starting from compound **1** (10 mg) and using acetone-d_6.

Registry No.—**1**, 34546-48-0; **2**, 34546-49-1; **3**, 34546-50-4; **4**, 34578-22-8; **7**, 34546-51-5.

Acknowledgments.—Our thanks are extended to Dr. Asher Mandelbaum for his help in the interpretation of mass spectra. This work was supported by grant AM 05098 from the National Institutes of Health, Public Health Service.

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Halo Sugar Nucleosides. III.[1] Reactions for the Chlorination and Bromination of Nucleoside Hydroxyl Groups

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The replacement of various hydroxyl functions in the sugar moiety of nucleosides by chlorine or bromine can be achieved through reaction with carbon tetrahalides and triphenylphosphine in DMF or DMAC. The reactions with primary hydroxyl groups are rapid and efficient while reactions of the secondary hydroxyl groups of 2′-deoxy nucleosides are slower. In the latter case, the chlorination reaction occurs principally with inversion of configuration while bromination proceeds mainly with retention of configuration. Pyrimidine nucleosides containing a free, *cis*-2′,3′-diol undergo quite selective chlorination of the 2′-hydroxyl function with retention of configuration. Mechanisms are discussed for these reactions. The nature of some side reactions between carbon tetrahalides, triphenylphosphine, and DMF are discussed. A recently described preparation of 3′-chloro-3′-deoxyuridine has been reexamined and found to give predominantly 5′-*O*-acetyluridine and derivatives of 2′-chloro-2′-deoxyuridine.

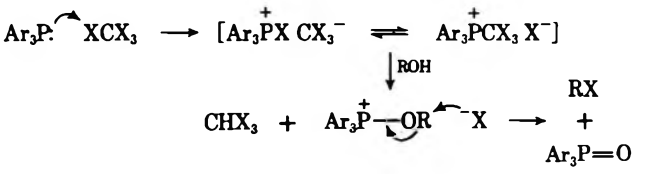
In recent papers from this laboratory, the reactions of methyltriphenoxyphosphonium iodide with suitably protected nucleosides has been shown to lead to the efficient replacement of either primary or secondary hydroxyl groups by iodo functions.[1,2] The resulting iodo sugar nucleosides can then be used in a variety of reactions leading to deoxy, amino, and unsaturated derivatives. In the present paper we outline the use of several reagents suitable for the related conversion of nucleoside hydroxyl groups to chloro or bromo functions. The resulting products are once again of interest as synthetic intermediates and, in some cases, can also be of primary biological interest.[3-6]

Previously the preparation of chloro and bromo sugar nucleosides has been achieved principally *via* nucleophilic displacement of sulfonyl esters,[7] opening of O^2,2′-cyclouridine with hydrogen halides[8] or, more recently, by direct halogenation of primary hydroxyl groups with Vilsmeier–Haack type complexes derived from thionyl halides with dimethylformamide (DMF)[9] or hexamethylphosphoramide.[10]

Recently considerable interest has centered upon the facile chlorination of hydroxyl groups by reaction with carbon tetrachloride and triphenylphosphine.[11] This type of reaction, which can also be conducted using trialkylphosphine,[12] has been applied to the chlorination and bromination of a few carbohydrates.[11,13] In this paper we describe the application of these and some related reagents to the halogenation of nucleoside hydroxyl groups.[14,15]

While precise mechanistic studies are still lacking, it is generally accepted that these reactions proceed *via* an ionic mechanism as shown below in Scheme I.[16]

SCHEME I



Our first objective was to compare the relative efficiencies of different carbon tetrahalides. Thus, 2′,3′-*O*-isopropylideneuridine (**1**) was treated under essentially identical conditions with 1 molar equiv each of triphenylphosphine and either CCl_4, CBr_4, or CI_4 in DMF at room temperature. By thin layer chromatography it was shown that the 5′-chloro (**2a**), 5′-bromo (**2b**), and 5′-iodo (**2c**) nucleosides were formed in yields of 86, 71, and 37% after 18 hr and the crystalline products were isolated in yields of 70, 55, and 17%, respectively. While no effort has been made to optimize yields and the above reactions were done using only 1 molar equiv of each reactant, it is clear that these methods are quite suitable for the chlorination and bromination of the primary hydroxyl groups of nucleosides. The iodination reaction, however, is poor under these conditions and rather similar results were obtained by others during halogenation of lincomycin derivatives.[13b]

For preparation of the 5′-iodo nucleoside **2c**, the use of methyltriphenoxyphosphonium iodide is much to be preferred.[1,2] Successful iodination of **1** was also achieved using iodotriphenylphosphonium iodide,[17,18] prepared from iodine and triphenylphosphine in DMF, **2c** being obtained in 59% yield.

(1) For part II, see J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, **35**, 2868 (1970).
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(6) R. Duschinsky, H. Walker, and J. Kára, Abstracts, 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969, MEDI-68.
(7) See, *e.g.*, (a) A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 816 (1955); (b) W. Jahn, *Chem. Ber.*, **98**, 1705 (1965).
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(12) J. Hooz and S. S. H. Gilani, *ibid.*, **46**, 86 (1968).
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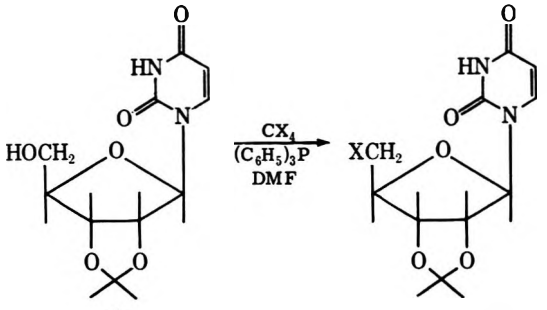
(14) This work has been summarized. See J. P. H. Verheyden and J. G. Moffatt, Abstracts, Joint CIC–ACS Conference, Toronto, Ontario, May 1970, Carbo 10.
(15) Very recently the chlorination or bromination of 2′,3′-*O*-isopropylideneinosine has been described: K. Haga, M. Yoshikawa, and T. Kato, *Bull. Chem. Soc. Jap.*, **43**, 3922 (1970).
(16) J. B. Lee and I. M. Downie, *Tetrahedron*, **23**, 359 (1967).
(17) K. Issleib and W. Seide., *Z. Anorg. Allg. Chem.*, **288**, 201 (1956).
(18) Related chlorination and bromination of alcohols has been described by G. A. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chung, *J. Amer. Chem. Soc.*, **86**, 964 (1964).

As will be seen later, the failure to iodinate **1** with carbon tetraiodide and triphenylphosphine in DMF is probably, at least in part, due to side reactions involving DMF. In support of this it was shown that a similar reaction using pyridine as the solvent gave **2c** in 76% yield. The use of triphenylphosphine and *N*-iodosuccinimide[19] gave poor results.

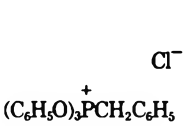


1 **2a**, X = Cl; **b**, X = Br; **c**, X = I

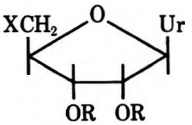
While iodination reactions using carbon tetraiodide are preferably not carried out in DMF, the latter solvent is generally well suited for chlorination and for bromination of primary alcohols (see later). The chlorination of **1** to **2a** is also quite satisfactory in hexamethylphosphoramide (HMPT) but does not proceed in dimethyl sulfoxide. Polar solvents such as DMF, dimethylacetamide (DMAC), and HMPT permit satisfactory reactions at room temperature, while the use of solvents such as carbon tetrachloride, in which nucleosides are frequently poorly soluble, normally requires heating.[13]

Chlorination of **1** could also be readily achieved in 70% yield *via* reaction with benzyltriphenoxyphosphonium chloride (**3**)[20] in DMF, but, since the reagent is a syrup that is difficult to handle and store, the use of carbon tetrachloride and triphenylphosphine is preferred.

Since the reaction conditions remain relatively neutral, particularly if the reaction is finally quenched with methanol rather than water, common protecting groups on the sugar prove to be stable. Thus, reaction of 2′,3′-di-*O*-acetyluridine (**4a**) readily gave 2′,3′-di-*O*-acetyl-5′-chloro-5′-deoxyuridine (**4b**) in 50% yield even on a small scale.

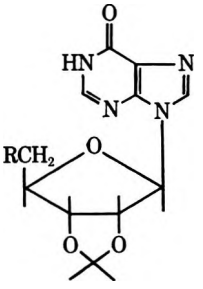


3

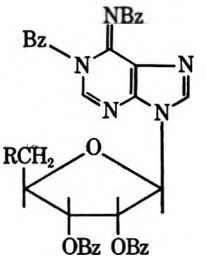


4a, R = Ac; X = OH; **b**, R = Ac; X = Cl; **c**, R = H; X = OH; **d**, R = H; X = Br; **e**, R = H; X = Cl

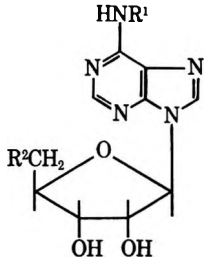
In a recent paper[15] the chlorination of 2′,3′-*O*-isopropylideneinosine (**5a**) to the corresponding 5′-chloro-5′-deoxy compound (**5b**) was achieved in high yield through reaction with triphenylphosphine and carbon tetrachloride in triethyl phosphate at 100°. These authors report, however, that the reaction did not proceed using DMF as solvent. This claim is in contrast to our results where chlorination in DMF at room temperature led to crystalline **5b** in 80% yield. In a similar way, the reaction of **5a** with carbon tetrabromide and triphenylphosphine in dimethylacetamide (DMAC) gave the 5′-bromo compound **5c** in 49% yield. In this latter case, DMAC was used rather than DMF in an effort to reduce the side reactions involving DMF. Chlorination of N^1,N^6,2′-*O*,3′-*O*-tetrabenzoyladenosine (**6a**)[21] also proceeded smoothly, giving the corresponding 5′-chloro-5′-deoxy nucleoside (**6b**) in 86% yield. Treatment of the latter compound with methanolic ammonium hydroxide at 23° for 3 hr removed the 2′-*O*, 3′-*O*, and N^1 benzoyl groups fairly selectively, giving crystalline N^6-benzoyl-5′-chloro-5′-deoxyadenosine (**7a**) in 46% yield. More prolonged hydrolysis removed all four benzoyl groups, giving 5′-chloro-5′-deoxyadenosine (**7b**) which, from its nmr spectrum, was clearly very pure but which consistently showed a broad melting point lower than that previously described for this compound.[10] This melting behavior is entirely to be expected for **7b**, since in the absence of an N^6-benzoyl group, the thermal formation of N^3,5′-cycloadenosine is a facile process.[2,22]



5a, R = OH; **b**, R = Cl; **c**, R = Br



6a, R = OH; **b**, R = Cl



7a, R^1 = Bz; R^2 = Cl; **b**, R^1 = H; R^2 = Cl

Fairly selective 5′ halogenation of unprotected nucleosides can also be achieved. Thus, free uridine and thymidine were directly converted into their 5′-bromo (**4d**) and 5′-chloro (**18c**)[23] derivatives in yields of 55 and 73% by reaction with 2 equiv of the appropriate carbon tetrahalide and triphenylphosphine. Attempted selective chlorination of cytidine was complicated by signifi-

(19) A related bromination of simple alcohols has been described by S. Tripett, *J. Chem. Soc.*, 2337 (1962), and has been applied to some carbohydrates and nucleosides: M. M. Ponpipom and S. Hanessian, *Carbohyd. Res.*, **18**, 342 (1971).

(20) S. R. Landauer and H. N. Rydon, *J. Chem. Soc.*, 2224 (1953). This reagent is more conveniently prepared than the corresponding methyl derivative due to the volatility of methyl chloride.

(21) M. Smith, D. H. Rammler, I. H. Goldberg, and H. G. Khorana, *J. Amer. Chem. Soc.*, **84**, 430 (1962).

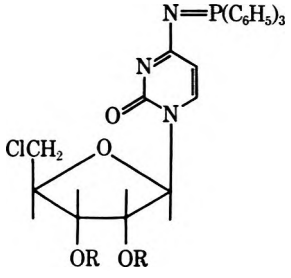
(22) V. M. Clark, A. R. Todd, and J. Zussman, *J. Chem. Soc.*, 2952 (1951).

(23) D. M. Brown, W. Cochran, E. H. Medlin, and S. Varadarajan, *ibid.*, 4873 (1956).

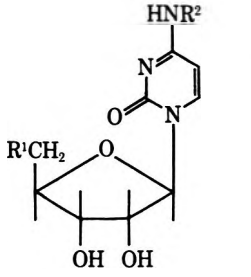
cant side reactions involving the 4-amino group on the cytosine ring. Many products were formed, including one crystalline material considered to be the iminophosphorane **8a**. The location of the chlorine function at $C_{5'}$ in **8a** was indicated by periodate oxidation and was confirmed by nmr spectroscopy, which showed the expected 1.3 ppm downfield shifts of the $C_{2'}$ and $C_{3'}$ protons upon acetylation to **8b**. A related formation of heterocyclic iminophosphoranes through reactions of aminotriazines with triphenylphosphine and chlorine has been described.[24]

This side reaction can be avoided by prior protection of the cytosine amino group, and selective chlorination of N^4-acetylcytidine (**9a**) gave crystalline N^4-acetyl-5′-chloro-5′-deoxycytidine (**9b**) in 58% yield. The presence of a free 2′,3′-diol was confirmed by a positive periodate test and by a 1.3 ppm downfield shift of the nmr resonance due to the $C_{2'}$ and $C_{3'}$ protons upon addition of trichloroacetyl isocyanate[25] to a solution of **9b** in DMF-d_7. Deacetylation of **9b** with ammonium hydroxide rapidly gave 5′-chloro-5′-deoxycytidine (**9c**)[10] in essentially quantitative yield.

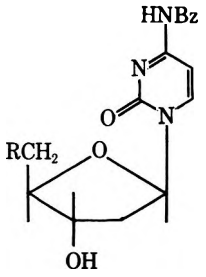
On the basis of tlc examination, the selective 5′-chlorination of N^4-benzoyl-2′-deoxycytidine (**10a**)[26] appears to proceed in high yield. In several experiments, however, the yield of crystalline **10b** isolated following preparative tlc was only about 10%. This poor yield may well be associated with inefficient elution from the silica due to the very low solubility of **10b**.



8a, R = H
b, R = Ac



9a, R^1 = OH; R^2 = Ac
b, R^1 = Cl; R^2 = Ac
c, R^1 = Cl; R^2 = H



10a, R = OH
b, R = Cl

The halogenation of secondary hydroxyl groups using reagents such as methyltriphenoxyphosphonium iodide[2] or combinations of triphenylphosphine and carbon tetrahalides[12,27] is known to normally proceed with inversion of configuration. Our earlier work, however, has shown that iodination of the 3′-hydroxy function in thymidine derivatives occurs with retention of configuration, this being explained by intervention of an O^2,3′-anhydro nucleoside as an intermediate.[1] It has now been shown that reaction of 5′-*O*-*p*-nitrobenzoylthymidine (**11a**) with triphenylphosphine and iodine also leads to 3′-deoxy-3′-iodo-5′-*O*-*p*-nitrobenzoylthymidine (**14a**) with complete retention of stereochemistry. The reaction is, however, sluggish and the crystalline product was isolated in only 47% yield. There was no indication of the formation of isomeric products.

The chlorination of 5′-*O*-tritylthymidine (**11b**) using triphenylphosphine and carbon tetrachloride in DMF at room temperature was quite different in that two crystalline, isomeric 3′-chloro-3′-deoxy nucleosides were formed. These were separated by preparative tlc and the less polar isomer (15% yield) was shown to have the erythro configuration **14b** by its identity with the product formed in 70% yield from authentic O^2,3′-anhydro-1-(2′-deoxy-5′-*O*-trityl-β-D-*threo*-pentofuranosyl)-thymine (the conjugate base of **13**, R = Tr)[1] and pyridine hydrochloride in DMF. The more polar, major product, isolated in 35% yield, retained its 5′-*O*-trityl function, and nmr decoupling studies clearly showed the retention of both $C_{2'}$ protons as well as of the $C_{3'}$, $C_{4'}$, and $C_{5'}$ protons. Accordingly, it must be assigned the structure 1-(3-chloro-2,3-dideoxy-5-*O*-trityl-β-D-*threo*-pentofuranosyl)thymine (**15a**). Both **14b** and **15a** were readily detritylated to the corresponding 3′-chloro nucleosides **14c** and **15b**.

It seems clear that the 3′-oxyphosphonium intermediate **12** can react in two different ways depending upon the nature of the halide ions present. In the case of iodide ion, both the size of the anion and its relatively low nucleophilicity in aprotic solvents such as DMF[28] conspire to prevent halide attack at $C_{3'}$ from the relatively hindered β face. Accordingly, the alternative SN2 displacement by the C_2 carbonyl group of the thymine ring takes precedence, leading to the O^2,3′-anhydro nucleoside **13**. As described previously,[1] **13** is then opened by halide ion, leading to the observed 3′-deoxy-3′-iodo-5′-*O*-tritylthymidine (**14d**) with overall retention of configuration. On the other hand, in the presence of chloride ion, which is both smaller and more nucleophilic than iodide in DMF,[27] direct SN2 displacement of the oxyphosphonium function by halide ion can compete favorably with the intramolecular process. Accordingly, the chlorination reaction leads principally to the inverted *threo*-3′-chloro derivative **15a** and to smaller amounts of **14b**.

The threo configuration of **15a** was confirmed by an independent synthesis of this compound from **14d** and lithium chloride in hot DMF. Here, once again, chloride ion can apparently compete favorably with the thymine carbonyl group in SN2 displacement of the 3′-iodo function. Treatment of **14d** with excess lithium chloride in DMF at 23° for 4 days led to no **15a**, thus ruling out **14d** as an intermediate in the formation of the threo isomer.

The reaction of free thymidine led, as expected, to initial chlorination at the primary 5′ position followed by slower reactions. Using 3 equiv of triphenylphos-

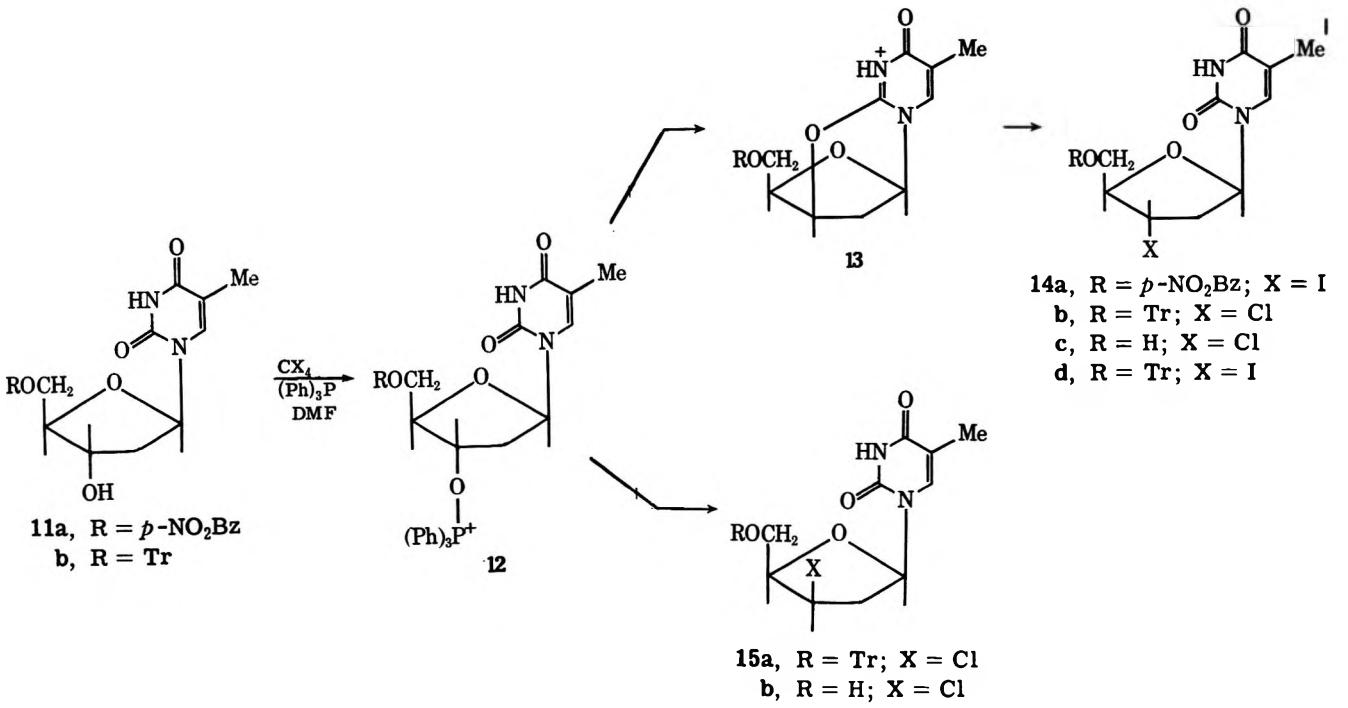
(24) (a) G. Gotsmann and M. Schwarzmann, *Justus Liebigs Ann. Chem.*, **729**, 106 (1969); (b) H. W. Roesby and H. H. Giere, *Chem. Ber.*, **102**, 2330 (1969).

(25) V. W. Goodlet, *Anal. Chem.*, **37**, 431 (1965).

(26) B. A. Otter and J. J. Fox in "Synthetic Procedures in Nucleic Acid Chemistry," Vol. 1, W. W. Zorbach and R. A. Tipson, Ed., Interscience, New York, N. Y., 1968, p 285.

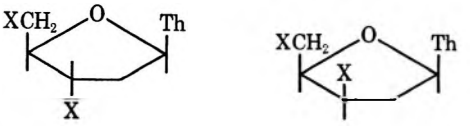
(27) (a) D. Brett, I. M. Downie, J. B. Lee, and M. F. S. Matough, *Chem. Ind. (London)*, 1017 (1969); (b) R. G. Weiss and E. I. Snyder, *J. Org. Chem.*, **35**, 1627 (1970).

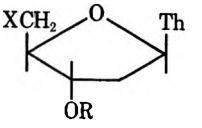
(28) W. M. Weaver and J. D. Hutchinson, *J. Amer. Chem. Soc.*, **86**, 261 (1964).



phine and an excess of carbon tetrachloride in DMF, two major nucleoside products were, once again, found and isolated in crystalline form by preparative tlc. The minor product, isolated in only 5% yield, had a melting point identical with that described for 3′,5′-dichloro-3′,5′-dideoxythymidine (**16a**) prepared previously by a different route and convincingly characterized by reconversion to the 5′-chloro-5′-deoxy-O^2,3′-anhydro nucleoside with base.[29] The major product, in 63% yield, was also a 3′,5′-dichloro nucleoside by nmr studies and is, accordingly, 1-(3,5-dichloro-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)thymine (**17a**). Clearly, the smaller size of the 5′-chloro group as compared with the 5′-*O*-trityl derivative makes direct SN2 displacement of the 3′-oxyphosphonium group by chloride ion an even more preferred process relative to anhydro nucleoside formation.

The dibromination of thymidine using triphenylphosphine and carbon tetrabromide was a much less efficient process, since even after 7 days reaction, 5′-bromo-5′-deoxythymidine (**18a**)[30] was isolated in 60% yield. Only small amounts of dibromo compounds were formed, the known erythro isomer **16b**[30] being obtained in 12% yield and the threo isomer **17b** in 4% yield. In spite of the low yields during bromination of the secondary 3′-hydroxy group, it is clear that the process with retention of configuration (*via* the anhydro nucleoside) is preferred over that leading to inversion. The increasing proportion of products with the threo configuration as one considers the iodination, bromination, and chlorination of thymidine derivatives can thus be directly related to the decreasing sizes and increasing nucleophilicities in DMF of the corresponding halide ions.





Further support for the stereochemical assignments of the various 3′-halo nucleosides above comes from an examination of the 100-MHz nmr spectra of these compounds. It has previously been noted[1] that the nmr spectra of many differently substituted 1-(2-deoxy-β-D-pentofuranosyl)thymines possessing the erythro configuration show very similar chemical shifts for the $C_{2'a}$ and $C_{2'b}$ protons which appear as partially or completely overlapping signals. On the other hand, compounds with the threo configuration show chemical shift differences of 0.5–1 ppm for these protons which then appear as well-separated ABXY patterns. While a discussion of the nmr spectra of many such compounds will appear shortly,[31] it is sufficient for the moment to say that the various pairs of 3′-halogenated compounds (*e.g.*, **14** and **15**, **16** and **17**) can be readily distinguished and characterized by this means.

While chlorination of both primary and secondary hydroxyl groups by this route is an efficient process, the low yields observed during bromination at the 3′ position of thymidine can be explained, at least in part, by the isolation of a by-product from this reaction. This crystalline substance behaved as an ultraviolet-absorbing cation upon electrophoretic examination and on the basis of its very simple nmr spectrum is considered

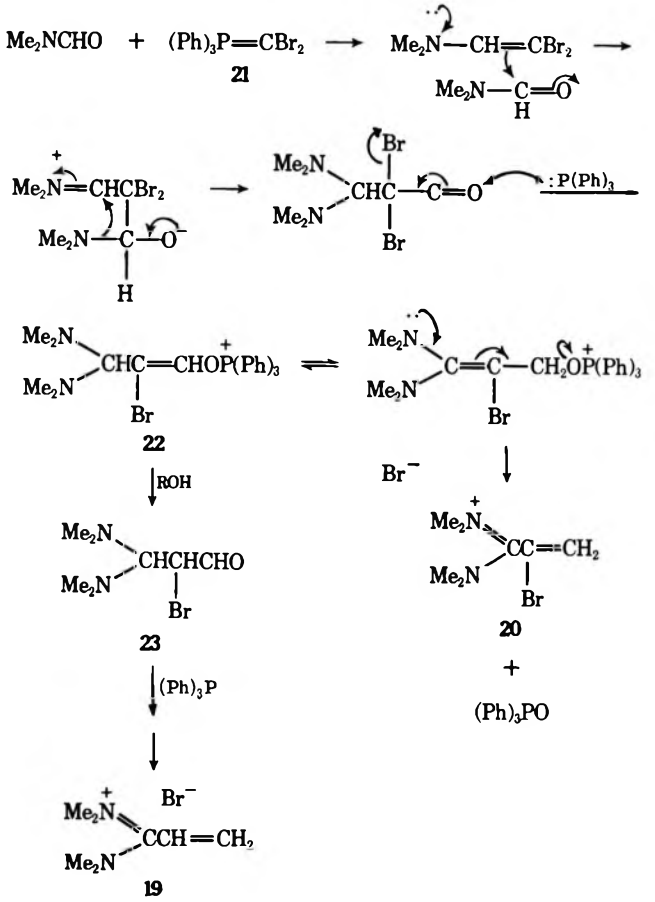
(29) Y. Mizuno, T. Ueda, K. Ikeda, and K. Miura, *Chem. Pharm. Bull.*, **16**, 262 (1968).

(30) A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 816 (1955).

(31) J. P. H. Verheyden, M. L. Maddox, and J. G. Moffatt, in preparation.

to be *N,N,N′,N′*-tetramethylacrylamidmium bromide (**19**). This compound crystallizes as a tenacious 2:1 complex with carbon tetrabromide, the presence of the latter confirmed by analysis, quantitative glc, and mass spectrometry.

In the absence of thymidine, a solution of triphenylphosphine and carbon tetrabromide in DMF deposits a crystalline compound similar to **19** but lacking one vinyl proton. This compound is assigned the structure **20** and once again crystallizes with 0.5 equiv of carbon tetrabromide. From this same reaction, **19** was also isolated in addition to large amounts of triphenylphosphine oxide and dimethylamine hydrobromide. Several relatively complex mechanisms can be suggested for the formation of **19** and **20** involving initial reaction of DMF with the dibromomethylenephosphorane (**21**) known to be formed from triphenylphosphine and carbon tetrabromide.[32] The use of triphenylphosphine and carbon tetrabromide in a ratio of 2:1, conditions known to favor the formation of **21** in other solvents,[32] leads to increased amounts of **19**. A suggested mechanism follows.



In the presence of an alcohol the oxyphosphonium salt **22** can undergo solvolysis with attack on phosphorus[33] giving the bromo aldehyde **23** and $(Ph_3)POR^+$. Subsequent attack by triphenylphosphine upon the oxygen of **23** can then give the debrominated product **19** by a process similar to that used to form **19**.[34]

(32) (a) F. Ramirez, N. B. Desai, and N. McKelvie, *J. Amer. Chem. Soc.*, **84**, 1745 (1962); (b) R. Rabinowitz and R. Marcus, *ibid.*, **84**, 1312 (1962).

(33) A. J. Speziale and R. D. Partos, *ibid.*, **87**, 5068 (1965).

(34) For a review of the reactions of α-halocarbonyl compounds with phosphorus derivatives, see (a) A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier, New York, N. Y., 1967, p 117; (b) B. Miller in "Topics in Phosphorus Chemistry," Vol. 2, M. Grayson and E. J. Griffith, Ed., Interscience, New York, N. Y., 1965, p 133.

The low yields achieved during iodination of even primary hydroxyl groups (*e.g.*, **1**) using carbon tetraiodide and triphenylphosphine in DMF is probably a reflection of an even greater tendency toward side reactions such as those above. In support of this idea, we have found that a comparable reaction of **1** using pyridine rather than DMF gave **2c** in 76% yield. As was the case using methyltriphenoxyphosphonium iodide,[1] however, it is likely that the use of a basic solvent such as pyridine will not facilitate the halogenation of nucleoside secondary hydroxyl groups, since nucleophilic opening of anhydro nucleosides such as **13** is known to be acid catalyzed.

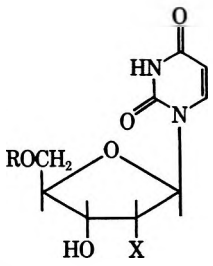
Our earlier work showed that iodination of vicinal diols using methyltriphenoxyphosphonium iodide failed due to nucleophilic displacement of phenolate ion from the oxyphosphonium intermediate by the adjacent hydroxyl group.[1] Since such a displacement is not possible using oxytriphenylphosphonium intermediates, the present methods should be suitable for use with cis vicinal diols. Accordingly, the reaction of 5′-*O*-acetyluridine (**24a**) with triphenylphosphine and carbon tetrachloride in DMF was found to give crystalline 5′-*O*-acetyl-2′-chloro-2′-deoxyuridine (**24b**) in 38% yield. The structure of **24b** was deduced by deacetylation to the known 2′-chloro-2′-deoxyuridine (**24c**)[35] and was confirmed by nmr spectroscopy. Thus, the presence of a free 3′-hydroxyl group was demonstrated by the sharpening of the signal due to $C_{3'}H$ (confirmed by decoupling studies) upon addition of D_2O. In a similar way, the direct chlorination of free uridine gave 17% of 5′-chloro-5′-deoxyuridine (**4e**)[9] and 68% of crystalline 2′,5′-dichloro-2′,5′-dideoxyuridine (**25**). Once again, the free hydroxyl group of **25** was located at $C_{3'}$ by decoupling experiments, irradiation of $C_{3'}H$ causing the D_2O-exchangeable doublet at 6.10 ppm ($C_{3'}OH$) to collapse to a singlet, and by acetylation which led to a 1 ppm downfield shift of $C_{3'}H$ but to only minor shifts of the other sugar protons. The ribo configuration of **25** was confirmed by further chlorination of authentic **24c**, which gave crystalline **25** identical with that above.

The quite selective reactions of the $C_{2'}$-hydroxyl groups in **24a** and in free uridine were also apparent in the cytidine series, since reaction of N^4-benzoylcytidine (**26a**)[36] gave 30% of N^4-benzoyl-5′-chloro-5′-deoxycytidine (**26b**) and N^4-benzoyl-2′,5′-dichloro-2′,5′-dideoxycytidine (**26c**) in 41% yield. The former compound was, as expected, periodate positive, while the free 3′-hydroxyl of **26c** was confirmed by acetylation giving **26d** which showed a 0.85 ppm downfield shift of $C_{3'}H$ relative to **26c**.

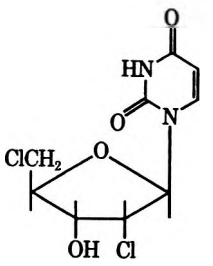
While we have provided convincing evidence that the 2′-chloro function of **24b** and of **25** has, indeed, the ribo configuration arising *via* an O^2,2′-anhydro nucleoside intermediate, the configuration at $C_{2'}$ in **26b** is based essentially upon analogy with the results in the uridine series. The selective reactivity of the 2′-hydroxyl group in 2′,3′-diols such as uridine, **24a**, and **26a** finds analogy in the well-known selective 2′-tosylation of 5′-

(35) (a) J. F. Codington, I. L. Doerr, and J. J. Fox, *J. Org. Chem.*, **29**, 558 (1964); (b) P. J. Cushley, J. F. Codington, and J. J. Fox, *Can. J. Chem.*, **46**, 1131 (1968).

(36) K. A. Watanabe and J. J. Fox, *Angew. Chem., Int. Ed. Engl.*, **5**, 579 (1966).



24a, R = Ac; X = OH
b, R = Ac; X = Cl
c, R = H; X = Cl



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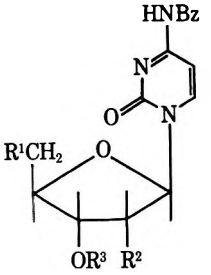
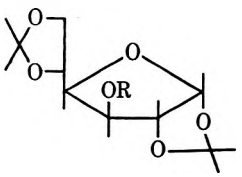


26a, $R^1 = R^2 = OH$; $R^3 = H$
b, $R^1 = Cl$; $R^2 = OH$; $R^3 = H$
c, $R^1 = R^2 = Cl$; $R^3 = H$
d, $R^1 = R^2 = Cl$; $R^3 = Ac$

substituted uridine derivatives,[37] and the preferential formation of 2′-*O*-methyl nucleosides using diazomethane.[38] While we cannot totally rule out the formation of 3′-halogenated nucleosides, their formation, if at all, must be in very low yield.

In the past, all efforts to directly halogenate the 3′-hydroxyl function of 1,2,5,6-di-*O*-isopropylidene-α-D-glucofuranose (**27a**) have been accompanied by acetal migration and have led to 6-deoxy-6-halo-1,2,3,5-di-*O*-isopropylidene-α-D-glucofuranoses.[13,39] We have found that reaction of **27a** with carbon tetrachloride and triphenylphosphine in DMF at room temperature leads to a major product that does not contain chlorine and is identical with the 3′-*O*-formyl derivative **27b** prepared using formic–acetic anhydride. Here, once again, the use of DMF as solvent can lead to by-products, but comparable reactions using other solvents have not been studied. It should be recalled that chlorination with inversion of configuration of the corresponding 1,2,5,6-di-*O*-isopropylidene-α-D-allofuranose isomer proceeds slowly, but without difficulty, in refluxing carbon tetrachloride.[13] The formation of **27b** has also been

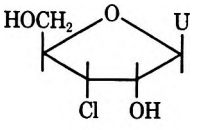


27a, R = H
b, R = CHO

suggested during reactions with chloromethylene dimethyliminium chloride,[39] but the product was not characterized.

(37) D. M. Brown, A. R. Todd, and S. Varadarajan, *J. Chem. Soc.*, 2388 (1956).
(38) (a) D. M. G. Martin, C. B. Reese, and G. F. Stephensen, *Biochemistry*, **7**, 1406 (1968); (b) J. B. Gin and C. A. Dekker, *ibid.*, **7**, 1413 (1968).
(39) S. Hanessian and N. R. Plessas, *J. Org. Chem.*, **34**, 2163 (1969), and references cited therein.

Finally, Dods and Roth[9,40] have reported the unusual observation that, while reaction of uridine with arsenic trichloride in DMF at 160° gave 5′-chloro-5′-deoxyuridine (**4e**) in 51% yield, the corresponding reaction in DMAC at 127° gave 3′-chloro-3′-deoxyuridine (**28**) in an isolated yield of 20%. A previous preparation of **28** was described by Kowollik and Langen[41] *via* the reaction of an O^2,3′-anhydro nucleoside with hydrogen chloride, but, more recently, Kikugawa and Ukita[42] have shown that the product of this reaction is indeed 1-(5-chloro-5-deoxy-β-D-xylofuranosyl)uracil arising by an intriguing rearrangement. We were, accordingly, interested in the mechanism by which **28** was formed, and, in particular, in the unusual role apparently played by DMAC. An examination of the data provided for **28**,[9,40] however, led to some doubts as to the correctness of the proposed structure. In particular, the ultraviolet absorption spectrum had an extinction coefficient of 7400 (*cf.* the value of 10,000 for normal uridine derivatives) and its chromatographic mobility was far from what would be expected. Thus, the R_f value of **28** (0.76) during paper chromatography in 1-butanol–water (86:14) was reported to be almost twice that of 5′-chloro-5′-deoxyuridine (R_f 0.42) in the same system. In our experience, the chromatographic mobilities of 5′-chloro- (**4e**) and 2′-chloro- (**24c**) uridines are very similar both by tlc and paper chromatography in many solvents, including that used by Dods and Roth[9,40] (R_f 0.44 and 0.48, respectively), and we would anticipate that **28** would also be comparable. An R_f value of 0.52 reported for 1-(5-chloro-5-deoxy-β-D-xylofuranosyl)uracil[41] is also very similar. We, accordingly, have carefully repeated this experiment four times using purified reagents and adhering closely to the described procedure. Paper and thin layer chromatography of the crude reaction mixtures do indeed generally resemble what has been described, but we have found the use of different solvent systems to greatly facilitate the preparative separation without altering the relative order of the bands.[43] The fastest band, corresponding to **28**, was, as described, rather unstable and during rechromatography underwent considerable degradation, but its major component was positively identified as 3′,5′-di-*O*-acetyl-2′-chloro-2′-deoxyuridine (**29**) by



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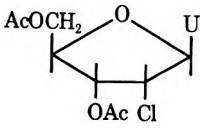

29

the identity of its melting point, infrared, and nmr spectra with those of an authentic sample.[35b,44] The degradation products of **29** resulted from deacetylation and included **24a** and **24c**, both identified by comparison with authentic samples. The other original bands were identified as **24c** and its monoacetyl derivatives, 5′-*O*-acetyluridine (43%) and some 5′-chloro-5′-deoxyuridine as well as 25% unreacted uridine. The various

(40) R. F. Dods, Ph.D. Thesis, University of Connecticut, 1968.
(41) G. Kowollik and P. Langen, *Chem. Ber.*, **101**, 235 (1968).
(42) K. Kikugawa and T. Ukita, *Chem. Pharm. Bull.*, **17**, 1775 (1969).
(43) As described, a reaction mixture from 2 g of uridine was separated on only five 8 × 8 in. plates with a 1 mm layer of silica, an extremely heavy loading for such a complex mixture.
(44) I. L. Doerr and J. J. Fox, *J. Org. Chem.*, **32**, 1462 (1967).

acetylated compounds undoubtedly arise *via* Vilsmeier-Haack type adducts of DMAC with arsenic trichloride.

1-(β-D-Xylofuranosyl)uracil (once again with an unexpected R_f value twice that of uridine while we find these compounds to have R_f 0.23 and 0.18 in the same system) was reported to be present in the reaction mixture and also to be the product of both acidic and alkaline treatment of **28**. We have been unable, by borate electrophoresis in the presence of an authentic sample, to detect the presence of this compound in the crude reaction mixtures either before or after acidic hydrolysis under the conditions described.[9,40]

Unfortunately, a sample of **28** was no longer available from Drs. Dods or Roth for comparison, but in our hands we have been unable to detect the formation of this compound by the route described. It is entirely possible that the above workers were the victims of a fortuitous circumstance since **29** contaminated by only 7–8% of ammonium chloride, a certain by-product of this reaction, would give an elemental analysis close to that observed. The structure **29** (R_f 0.76 in our hands) would adequately explain both the anomalous chromatographic mobility and the low extinction coefficient.[45] It cannot, however, explain the deviation in melting point between that reported for **28** and **29**, and a resolution of this question must await a reliable independent synthesis of **28**.[46]

Taken in conjunction with the use of reagents such as methyltriphenoxyphosphonium iodide,[1,2] the triphenylphosphine–carbon tetrahalide reagents make the synthesis of a wide range of halo sugar nucleosides possible. Work on some quite unrelated halogenating agents will be reported shortly.[47]

Experimental Section

General Methods.—The general methods used are similar to those described previously.[1] Melting points are recorded using a hot-stage microscope and are corrected. Assignments of sugar protons in nmr spectra are generally confirmed by decoupling experiments. Further confirmation of the structural assignments of most compounds was obtained from ORD and mass spectral data, the details of which are not reported. Nuclear magnetic resonance spectra are recorded in Tables I and II.

5′-Chloro-5′-deoxy-2′,3′-*O*-isopropylideneuridine (2a). A. Using Triphenylphosphine–CCl_4.—Carbon tetrachloride (176 mg, 1.16 mmol) was added to a solution of **1** (284 mg, 1 mmol) and triphenylphosphine (262 mg, 1 mmol) in anhydrous DMF (10 ml). After 18 hr at 23° the solvent was evaporated *in vacuo* and the residue was purified by preparative tlc using CCl_4–acetone (3:2). Elution of the major band followed by crystallization from chloroform–hexane gave 212 mg (70%) of **2a**, mp 180–181° (reported[9] mp 175–177°), λ_{max}^{MeOH} 259 mμ (ε 10,600).

Anal. Calcd for $C_{12}H_{15}N_2O_5Cl$ (302.7): C, 47.61; H, 4.99; N, 9.26; Cl, 11.72. Found: C, 47.67; H, 4.95; N, 9.11; Cl, 11.58.

B. Using Benzyltriphenoxyphosphonium Chloride (3).—A solution of **1** (426 mg, 1.5 mmol) and **3** (1.5 g, 3 mmol)[20] in anhydrous DMF (5 ml) was kept at room temperature for 2.5 hr. After addition of methanol (1 ml) the solvent was evaporated and the residue was purified by preparative tlc using CCl_4–ethyl acetate (9:1). Elution of the major band and crystallization from chloroform–hexane gave 316 mg (70%) of **2a** identical with that from A.

5′-Bromo-5′-deoxy-2′,3′-*O*-Isopropylideneuridine (2b).—A solution of **1** (284 mg, 1 mmol), triphenylphosphine (262 mg, 1 mmol), and CBr_4 (545 mg, 1.05 mmol) in anhydrous DMF (10 ml) was kept at 23° for 18 hr. It was then evaporated to dryness and purified as for **2a** above, giving, after crystallization from chloroform–hexane, 191 mg (55%) of **2b**, mp 184–186° (reported[23] mp 184–186°), λ_{max}^{MeOH} 259 mμ (ε 10,200).

Anal. Calcd for $C_{12}H_{15}N_2O_5Br$ (347.18): C, 41.51; H, 4.35; N, 8.07. Found: C, 41.57; H, 4.78; N, 7.69.

5′-Bromo-5′-deoxyuridine (4d).—A solution of uridine (244 mg, 1 mmol), triphenylphosphine (524 mg, 2 mmol), and CBr_4 (664 mg, 2 mmol) in DMF (5 ml) was kept for 24 hr at 23°, diluted with methanol, and evaporated to dryness. Preparative tlc using chloroform–methanol (85:15) gave a number of bands. Elution of the band faster than unreacted uridine gave 170 mg (55%) of **4d** which crystallized very slowly from methanol, giving 85 mg (27%), mp 180–183° (reported[23] mp 182–184°), λ_{max}^{MeOH} 260 mμ (ε 9900).

5′-Chloro-5′-deoxythymidine (18c).—A solution of thymidine (484 mg, 2 mmol), triphenylphosphine (700 mg, 2.7 mmol), and CCl_4 (1 ml, 10 mmol) in DMF (10 ml) was kept at 23° for 24 hr and then quenched with methanol. The solution was then evaporated and the residue was crystallized from methanol, giving pure **18c**. Preparative tlc of the mother liquors using chloroform–acetone (7:3) followed by recrystallization of the combined products from methanol gave 380 mg (73%) of **18c**, mp 193–195°, λ_{max}^{MeOH} 266 mμ (ε 9400).

Anal. Calcd for $C_{10}H_{13}N_2O_4Cl$ (260.68): C, 46.07; H, 5.02; N, 10.75. Found: C, 46.35; H, 5.17; N, 10.78.

5′-Deoxy-5′-iodo-2′,3′-*O*-isopropylideneuridine (2c). A. With Triphenylphosphine–Carbon Tetraiodide.—A solution of **1** (284 mg, 1 mmol), carbon tetraiodide (520 mg, 1 mmol), and triphenylphosphine (262 mg, 1 mmol) in pyridine (5 ml) was kept at room temperature for 16 hr and then evaporated to dryness. The residue was dissolved in chloroform, washed with aqueous sodium thiosulfate and water, dried, and purified by preparative tlc using CCl_4–ethyl acetate (65:35). Crystallization of the major product from chloroform–hexane gave 300 mg (76%) of **2c**, mp 166–167°, identical with an authentic sample.[2]

A similar reaction using anhydrous DMF (10 ml) as solvent gave crystalline **2c** in only 17% yield.

B. Using Triphenylphosphine and Iodine.—A solution of **1** (248 mg, 1 mmol), triphenylphosphine (262 mg, 1 mmol), and iodine (254 mg, 1 mmol) in anhydrous DMF (5 ml) was kept at room temperature for 24 hr, then evaporated to dryness. The residue was purified by preparative tlc using CCl_4–acetone (3:2) and the major product was crystallized from chloroform–hexane, giving 233 mg (59%) of **2c** identical with that from A.

2′,3′-di-*O*-Acetyl-5′-chloro-5′-deoxyuridine (4b).—A solution of **4a** (109 mg, 0.33 mmol), triphenylphosphine (88 mg, 0.33 mmol), and CCl_4 (0.1 ml, 1 mmol) in DMF (2 ml) was kept at 20° for 18 hr and evaporated to dryness. Preparative tlc using ethyl acetate followed by crystallization from chloroform–hexane gave 58 mg (50%) of **4b**, mp 152–154°, λ_{max}^{MeOH} 258 mμ (ε 9900).

Anal. Calcd for $C_{13}H_{15}N_2O_7Cl$ (346.5): C, 45.02; H, 4.33. Found: C, 44.86; H, 4.55.

Attempted Chlorination of Cytidine.—A solution of cytidine (243 mg, 1 mmol), triphenylphosphine (786 mg, 3 mmol), and CCl_4 (0.5 ml) in DMF (10 ml) was kept for 4 hr at 23°. After addition of methanol (3 ml) and evaporation to dryness, the residue was separated by preparative tlc using chloroform–methanol (93:7), giving triphenylphosphine oxide and three slower bands. The two slower bands were complex mixtures and elution of the faster band gave 140 mg (27%) of **8a**, mp 220.5–221.5° from methanol, λ_{max}^{MeOH} 289 mμ (ε 22,100).

Anal. Calcd for $C_{27}H_{25}N_3O_4PCl$ (521.93): C, 62.13; H, 4.82; N, 8.05. Found: C, 62.28; H, 4.72; N, 8.00.

Acetylation of this material with pyridine and acetic anhydride gave the chromatographically homogeneous 2′,3′-di-*O*-acetyl derivative (**8b**) which was not obtained crystalline. See Tables I and II for nmr.

N^4-Acetyl-5′-chloro-5′-deoxycytidine (9b).—A solution of **9a** (570 mg, 2 mmol), triphenylphosphine (570 mg, 2.2 mmol), and CCl_4 (1 ml, 10 mmol) in DMF (10 ml) was kept at 20° for 24 hr. Since unreacted **9a** remained, a further 285 mg of triphenylphosphine was added. After 24 hr methanol (1 ml) was added and the solvent was evaporated *in vacuo*, leaving a syrup that was dissolved in chloroform (10 ml). Addition of benzene (10 ml) gave a precipitate (625 mg) that was crystallized from methanol, giving 355 mg (58%) of **9b**, mp 217–218°, λ_{max}^{MeOH} 299 mμ (ε 7200), 248 (15,600), 214 (16,900).

(45) Recalculation of the reported ultraviolet data using the increased molecular weight of **29** raises the ε value from 7400 to 9800, a figure typical of uracil nucleosides.

(46) We have made our observations available to Drs. Dods and Roth, who agree with our conclusions: Dr. J. S. Roth, personal communication.

(47) Unpublished work by S. Greenberg, A. F. Russell, and J. G. Moffatt.

Table I

Nmr Chemical Shifts at 100 MHz

Compd	Solvent[a]	$C_{1'}H$	$C_{2'a}H$	$C_{2'b}H$	$C_{3'}H$	$C_{4'}H$	$C_{5'a}H$	$C_{5'b}H$	C_5H	C_6H	C_5Me	Other
2a	C	5.73 (d)	5.04 (dd)		4.92 (dd)	4.40 (dt)	3.73 (dd)	3.88 (dd)	5.82 (d)	7.36 (d)		1.42, 1.43 (CMe_2), 9.55 (br s, NH)
2b	C	5.65 (d)	5.00 (dd)		4.85 (dd)	4.36 (dt)	3.51 (dd)	3.66 (dd)	5.74 (d)	7.32 (d)		1.36, 1.57 (s, CMe_2), 7.69 (br s, NH)
4b	C	6.15 (d)	5.38 (m)		5.38 (m)	4.42 (m)	3.88 (2, br d)		5.85 (d)	7.56 (d)		2.09, 2.13 (s, Ac), 11.62 (br s, NH)
4d	P	6.58 (d)	4.76 (m)		5.57 (m)	4.57 (m)	3.96 (2, m)		5.81 (d)	7.85 (d)		
4e	P	6.64 (d)	4.80 (m)		4.65 (m)	4.65 (m)	4.12 (m)	4.12 (m)	5.84 (d)	7.90 (d)		
5b	P	6.49 (d)	5.54 (dd)		5.25 (dd)	4.60 (dt)	3.83 (dd)	3.98 (dd)	5.84 (d)			1.38, 1.59 (s, CMe_2), 8.32, 8.43 (C_2H), C_8H)
5c	P	6.51 (d)	5.57 (dd)		5.28 (dd)	4.65 (dt)	3.69 (dd)	3.86 (dd)				1.39, 1.59 (s, CMe_2), 8.35, 8.49 (C_2H, C_8H)
6b	C	6.57 (d)	6.25 (dd)		6.06 (dd)	4.79 (dt)	4.05 (2, br d)					7.45, 7.92 (m, Ar), 8.45, 8.73 (C_2H and C_8H)
7a	P	6.71 (d)	5.35 (dd)		4.94 (dd)	4.79 (dt)	4.08 (dd)	4.24 (dd)				7.45, 8.30 (m, Ar), 8.90 (s, 2, C_2H, C_8H)
7b	P	6.61 (d)	5.35 (dd)		4.91 (dd)	4.72 (dt)	4.06 (dd)	4.22 (dd)				8.18 (s, NH_2), 8.52, 8.57 (s, C_2H, C_8H)
8a	P	6.59 (d)	4.55 (m)		4.55 (m)	4.55 (m)	4.09 (m)	4.09 (m)	6.43 (d)	8.1 (d)		7.45, 8.1 (m, Ar)
8b	P	6.48 (d)	5.85 (m)		5.85 (m)	4.41 (m)	3.95 (d)	3.95 (d)	6.37 (d)	7.75–8.1		1.85, 1.96 (s, OAc), 7.4, 7.9 (m, Ar)
9b	P	6.60 (d)	4.82 (dd)		4.70 (m)	4.70 (m)	4.22 (2, m)		8.45 (d)	8.70 (d)		2.27 (s, NAc)
9c	P	6.64 (d)	4.6 (m)		4.6 (m)	4.6 (m)	4.13 (2, m)		6.00 (d)	7.93 (d)		8.4 (br s, NH_2)
10b	P	6.76 (dd)	2.45 (ddd)	2.89 (ddd)	4.76 (ddd)	4.54 (m)	4.02 (d)	4.02 (d)	7.71 (d)	8.33 (d)		7.48, 8.22 (m, Ar)
14b	C	6.34 (dd)	2.63 (dd)	2.63 (dd)	4.56 (dd)	4.19 (ddd)	3.40 (dd)	3.54 (dd)		7.53	1.50[d]	7.30 (m, Ar), 9.10 (br s, NH)
14c	P	6.80 (dd)	2.65 (ddd)	2.88 (ddd)	4.92 (ddd)	4.37 (dd)	4.01 (dd)	4.17 (dd)		8.00	1.82	
15a	C	6.15 (dd)	2.33 (ddd)	2.95 (ddd)	4.45 (m)	4.21 (m)	3.37 (dd)	3.61 (dd)			1.83	7.1–7.6 (m, Ar and C_6H)
15b	P	6.55 (dd)	2.56 (ddd)	3.10 (ddd)	4.91 (ddd)	3.4 (m)	3.40 (m)	3.40 (m)		7.87	1.94	
16a	C	6.30 (t)	2.63 (dd)	2.63 (dd)	4.4 (m)	4.4 (m)	3.90 (d)	3.90 (d)		7.40	1.93	
16b	C	6.25 (t)	2.73 (dd)	2.73 (dd)	4.38 (m)	4.38 (m)	3.75 (br d)	3.75 (br d)		7.40	1.92	9.60 (br s, NH)
17a	C	6.24 (dd)	2.43 (ddd)	3.08 (ddd)	4.65 (ddd)	4.27 (dt)	3.85 (d)	3.85 (d)		7.50	1.97	9.35 (br s, NH)
17b	C	6.21 (dd)	2.56 (ddd)	3.25 (ddd)	4.65 (ddd)	4.13 (ddd)	3.55 (dd)	3.70 (dd)		7.59	1.94	9.55 (br s, NH)
18a	P	6.83 (dd)	2.46–2.63 (m)	2.46–2.63 (m)	4.77 (dt)	4.44 (dt)	3.86 (d)	3.86 (d)		7.62	1.93	
18c	P	6.90 (t)	2.55 (m)	2.55 (m)	4.84 (m)	4.49 (dt)	4.03 (2, d)			7.67 (d)	1.92 (d)	
24b	A	6.10 (d)	4.65 (dd)		4.43 (br t)	4.20 (m)	4.20 (m)	4.20 (m)	5.74 (d)	7.72 (d)		1.08 (s, Ac), 5.00 (br s, 3′-OH), 10.15 (br s, NH)
25	D	6.03 (d)	4.72 (dd)		4.15 (m)	4.15 (m)	3.90 (m)	3.90 (m)	5.72 (br d)[b]	7.66 (d)		6.10 (d, $J_{3',OH}$ = 6 Hz, $C_{3'}OH$)[c]
26b	D	5.89 (d)	3.9–4.3 (m)		3.9–4.3 (m)	3.9–4.3 (m)	3.9–4.3 (m)	3.9–4.3 (m)	7.39 (d)	8.19 (d)		7.60, 8.05 (m, Ar), 5.34, 5.60 (d, $J_{H,OH}$ = 5 Hz, $C_{2'}OH$, $C_{3'}OH$)
26c	P	6.72 (d)	5.27 (dd)		4.91 (dd)	4.76 (ddd)	4.17 (dd)	4.33 (dd)	7.74 (d)	8.44 (d)		7.55, 8.25 (m, Ar)
26d	P	6.60 (d)	5.48 (dd)		5.76 (dd)	4.46 (dt)	4.14 (m)	4.14 (m)	7.68 (d)	8.25 (dd)		2.05 (s, OAc)

[a] Solvents are acetone-d_6 (A), $CDCl_3$ (C), DMSO-d_6 (D), and pyridine-d_5 (P). [b] Becoming dd ($J_{6,NH}$ = 2 Hz) at 60° and a sharp doublet with D_2O. [c] Location of 3′-OH confirmed by acetylation which led to a 1.0 ppm downfield shift of $C_{3'}H$. [d] All thymidine derivatives show a roughly 1 Hz allylic coupling of C_5Me.

TABLE II
COUPLING CONSTANTS (cps) FOR COMPOUNDS IN TABLE I

Compd	$J_{1',2'a}$	$J_{1',2'b}$	$J_{2'a,2'b}$	$J_{2'a,3'}$	$J_{2'b,3'}$	$J_{3',4'}$	$J_{4',5'a}$	$J_{4',5'b}$	$J_{5'a,5'b}$	$J_{5,6}$
2a	2.0			6.5		3.5	5.5	5.5	11.5	8
2b	2.0			6.5		3	5.5	5.5	10	8
4b	6					*a*	4			8
4d	4.5			4.5		*a*	*a*			8
4e	4			*a*		*a*	*a*	*a*	*a*	8
5b	2.5			6		3	6	7	11	
5c	2			6		3	6	7	10	
6b	5.5			5.5		4	4			
7a	5			5		5	5	5	12	
7b	4.5			4.5		4.5	5	4.5	11	
8a	2.5			*a*		*a*	*a*	*a*	*a*	8
8b	4			*a*		*a*	5	5	*a*	7
9b	3.5			5.0	*a*	*a*	*a*	*a*	*a*	8
9c	3.0			*a*		*a*	*a*	*a*	*a*	7.5
10b	6.0	6.0	13	6.0	4.0	4.0	4			8
14b	6	6		6	6	5	2.5	2.5	11	
14c	6	6	14	7	6	5	3	2.5	12	
15a	3	7	16	1	1.5	*a*	4.5	6.5	10	
15b	4	7.5	15	2	6	3.5	*a*	*a*	*a*	
16a	6.5	6.5		6.5	6.5	*a*	*a*	*a*	*a*	
16b	6	6		6	6	*a*	2	2		
17a	4	8	15	1	6.5	3.5	6	6		
17b	3.5	8	16	1	6	3	7.5	6	10	
18a	6.5	6.5	*a*	3	3	3.5	5	5		
18c	7.5			*a*		5	4	4		
24b	5	5		5	5	5	*a*	*a*	*a*	8
25	7			4.5		*a*	*a*	*a*	*a*	8
26b	4			*a*		*a*	*a*	*a*	*a*	8
26c	3.5			5		6	3	3	12	8
26d	5			6		6	5.5	5.5		8

[a] Not resolved.

Anal. Calcd for $C_{11}H_{14}N_3O_5Cl$ (303.7): C, 43.50; H, 4.64; N, 13.83; Cl, 11.67. Found: C, 43.18; H, 4.39; N, 13.82; Cl, 11.65.

5'-Chloro-5'-deoxycytidine (9c).—Concentrated ammonium hydroxide (17.5 ml) was added to a solution of **9b** (1.06 g, 3.5 mmol) in methanol (17.5 ml) and briefly warmed to obtain a clear solution. After 10 min at 23° the mixture was evaporated to dryness and crystallized from methanol, giving 890 mg (97%) of **9c**, mp 163.5–164.5° (reported[10] mp 160–168° dec), $\lambda_{max}^{pH\ 1}$ 213 mμ (ε 9600), 279 (12,400).

Anal. Calcd for $C_9H_{12}N_3O_4Cl$ (261.67): C, 41.31; H, 4.62; N, 16.06; Cl, 13.55. Found: C, 41.10; H, 4.68; N, 15.93; Cl, 13.43.

N^4-Benzoyl-5'-chloro-2',5'-dideoxycytidine (10b).—A solution of 10a (658 mg, 2 mmol),[28] triphenylphosphine (1.5 g, 6 mmol), and CCl_4 (1.5 g, 10 mmol) in DMF (30 ml) was kept at 23° for 16 hr and then evaporated to dryness after addition of methanol (5 ml). The dried residue, which contained one major product by tlc, was purified by preparative tlc on three plates using chloroform–methanol (19:1). Elution of the major band (R_f 0.4) gave only 68 mg (10%) of **10b**, which was recrystallized from methanol, mp >300°, λ_{max}^{MeOH} 260 mμ (ε 23,000), 304 (10,000).

Anal. Calcd for $C_{16}H_{16}N_3O_4Cl$ (349.75): C, 54.94; H, 4.61; N, 12.01. Found: C, 54.56; H, 4.52; N, 12.00.

5'-Chloro-5'-deoxy-2',3'-*O*-isopropylideneinsoine (5b).—A solution of **5a** (308 mg, 1 mmol), triphenylphosphine (524 mg, 2 mmol), and CCl_4 (0.5 ml) in DMF (10 ml) was kept at 23° for 12 hr and then evaporated to dryness after addition of methanol. The residue was chromatographed on a column containing 100 g of Merck silicic acid deactivated with 6% water using a gradient of 0–10% methanol in chloroform. Evaporation of the pooled major peak and crystallization from methanol gave 260 mg (80%) of **5b**, mp 201–201.5° (reported[15] mp 195°), λ_{max}^{MeOH,H^+} 250 mμ (ε 10,800).

Anal. Calcd for $C_{13}H_{15}N_4O_4Cl$ (326.7): C, 47.78; H, 4.63; N, 17.15. Found: C, 47.54; H, 4.73; N, 17.05.

5'-Bromo-5'-deoxy-2',3'-*O*-isopropylideneinosine (5c).—A reaction between **5a** (616 mg, 2 mmol), triphenylphosphine (1.05 g, 4 mmol), and CBr_4 (664 mg, 2 mmol) in dimethylacetamide (10 ml) was worked up after 16 hr exactly as above for **5b**. The product in the major peak following triphenylphosphine oxide was crystallized from methanol, giving 365 mg (49%) of **5c**, mp 201–203° dec (reported[15] mp 194°), λ_{max}^{MeOH,H^-} 250 mμ (ε 9200).

Anal. Calcd for $C_{13}H_{15}N_4O_4Br$ (317.2): C, 42.06; H, 4.07; N, 15.09. Found: C, 41.87; H, 4.16; N, 15.03.

N^1,N^6-2'-*O*,3'-*O*-Tetrabenzoyl-5'-chloro-5'-deoxyadenosine (6b).—A solution of **6a** (1.32 g, 2 mmol),[21] triphenylphosphine (1.51 g, 6 mmol), and CCl_4 (0.84 ml, 8 mmol) in DMF (16 ml) was kept at room temperature for 24 hr. After addition of methanol the solvent was evaporated and the residue was purified by preparative tlc using benzene–ethyl acetate (2:1). Elution of the major band gave 1.20 g (86%) of **6b**, mp 155.5–156.5° after recrystallization from methanol, λ_{max}^{MeOH} 231 mμ (ε 39,900), 274 (20,700).

Anal. Calcd for $C_{38}H_{28}N_5O_7Cl$ (702.10): C, 65.00; H, 4.02; N, 9.98. Found: C, 64.99; H, 3.88; N, 9.84.

N^6-Benzoyl-5'-chloro-5'-deoxyadenosine (7a) and 5'-Chloro-5'-deoxyadenosine (7b).—Concentrated ammonium hydroxide (8 ml) was added to a solution of **6b** (520 mg) in methanol (50 ml). After 3 hr at 23° the mixture was evaporated to dryness and the residue was crystallized from methanol, giving 130 mg (46%) of **7a**, mp 166.5–167.5°, λ_{max}^{MeOH} 230 mμ (ε 13,200), 279 (19,000).

Anal. Calcd for $C_{17}H_{16}N_5O_4Cl$ (389.80): C, 52.38; H, 4.14; N, 17.97. Found: C, 52.18; H, 4.23; N, 17.88.

A separate sample of **6b** (720 mg) was treated as above for 2 days and then evaporated to dryness. Two recrystallizations from methanol gave 198 mg (68%) of **7b**, mp 140–165° (reported[10] mp 190° dec), λ_{max}^{MeOH} 258 mμ (ε 13,700).

Anal. Calcd for $C_{10}H_{12}N_5O_3Cl$ (285.69): C, 42.03; H, 4.23; N, 24.51. Found: C, 41.61; H, 4.70; N, 24.78.

Chlorination of 5'-*O*-tritylthymidine (11b).—A solution of **11b** (1.94 g, 4 mmol), triphenylphosphine (1.57 g, 4 mmol), and CCl_4 (0.84 ml, 8 mmol) in DMF (10 ml) was kept at 23° for 24 hr, diluted with methanol, and evaporated to dryness. Preparative tlc using methylene chloride–ethyl acetate (3:2) separated triphenylphosphine oxide from two major faster products. Elution of the faster band gave 300 mg (15%) of 3'-chloro-3'-deoxy-5'-*O*-tritylthymidine (**14b**), mp 144–146° from methanol–acetone, λ_{max}^{MeOH} 266 mμ (ε 9500).

Anal. Calcd for $C_{29}H_{27}N_2O_4Cl$ (503.0): C, 69.25; H, 5.41; Cl, 7.05. Found: C, 69.14; H, 5.55; Cl, 7.15.

Elution of the slower band and rechromatography using carbon tetrachloride–acetone (2:1) gave 700 mg (35%) of homogeneous 1-(3-chloro-2,3-dideoxy-5-*O*-trityl-β-D-*threo*-pentofuranosyl)thymine (**15a**), mp 203–205° from chloroform–hexane, λ_{max}^{MeOH} 265 mμ (ε 9600).

Anal. Calcd for $C_{29}H_{27}N_2O_4Cl$ (503.0): C, 69.25; H, 5.41; N, 5.57. Found: C, 69.14; H, 5.48; N, 5.44.

3′-Chloro-3′-deoxy-5′-*O*-tritylthymidine (14b).—A solution of O^2,3′-anhydro-1-(2-deoxy-5-*O*-trityl-β-D-*threo*-pentofuranosyl)-thymine (476 mg, 1 mmol)[47] and anhydrous pyridine hydrochloride (460 mg, 4 mmol) in DMF (10 ml) was kept at 23° for 4 days. After evaporation of the solvent, the residue was dissolved in chloroform, washed with water, dried, and evaporated to dryness. Crystallization from methanol gave 341 mg (70%) of **14b** identical in all ways with that above.

1-(3-Chloro-3-deoxy-5-*O*-trityl-β-D-*threo*-pentofuranosyl)thymine (15a).—A solution of **14d** (594 mg, 1 mmol) and lithium chloride (425 mg, 10 mmol) in DMF (10 ml) was heated at 100° for 30 min. The cooled solution was evaporated and the residue was dissolved in chloroform, filtered, and purified by preparative tlc using chloroform–ethyl acetate (65:35). The major slower moving band was eluted and crystallized from chloroform–hexane, giving **15a** (250 mg, 50%) that was identical with **15a** above by melting point and nmr spectroscopy.

3′-Chloro-3′-deoxythymidine (14c).—A suspension of **14b** (300 mg) in 80% acetic acid (10 ml) was heated at 100° for 30 min, giving a clear solution that was evaporated to dryness. Preparative tlc using ethyl acetate gave a major band containing 170 mg (75%) of **14c**, mp 181–182° from acetone–hexane,[48] λ_{max}^{MeOH} 266 mμ (ε 10,200).

Anal. Calcd for $C_{10}H_{13}N_2O_4Cl$ (260.68): C, 46.07; H, 5.02; N, 10.75. Found: C, 46.04; H, 5.11; N, 10.75.

1-(3-Chloro-2,3-dideoxy-β-D-*threo*-pentofuranosyl)thymine (15b).—Treatment of **15a** (700 mg) with 80% acetic acid exactly as for **14b** above gave 500 mg (83%) of **15b** as a homogeneous syrup, $\lambda_{max}^{pH\ 1}$ 268 mμ (ε 9100).

Anal. Calcd for $C_{10}H_{13}N_2O_4Cl$ (260.68): C, 46.07; H, 5.02; N, 10.75. Found: C, 46.49; H, 5.25; N, 11.07.

3′-Deoxy-3′-iodo-5′-*O*-*p*-nitrobenzoylthymidine (14a).—A solution of **11a** (300 mg, 0.76 mmol), triphenylphosphine (300 mg, 1.1 mmol), and iodine (254 mg, 1 mmol) in DMF (10 ml) was kept at 23° for 14 days and then evaporated to dryness. The residue was dissolved in chloroform, washed with aqueous sodium thiosulfate, and chromatographed on a column of silicic acid using a gradient (0–50%) of ethyl acetate in chloroform. Evaporation of the major peak and crystallization from chloroform–hexane gave 180 mg (47%) of **14a**, mp 154–156°, identical with an authentic sample.

Chlorination of Thymidine.—A solution of thymidine (1.94 g, 8 mmol), triphenylphosphine (6.3 g, 24 mmol), and CCl_4 (4 ml, 40 mmol) in DMF (30 ml) was kept at 23° for 10 days and then evaporated to dryness after addition of methanol. The residue (12 g) was dissolved in ethyl acetate and, after removal of 4 g of tripheny phosphine oxide, chromatographed on a column of silic acid (500 g). Elution with chloroform and then chloroform–ethyl acetate gave a total of 3.6 g of material contaminated with triphenylphosphine oxide. Preparative tlc using carbon tetrachloride:acetone (2:1) gave two main nucleoside-containing bands. Elution of the faster band and crystallization from ethanol gave 100 mg (5%) of 3′,5′-dichloro-3′,5′-dideoxythymidine (**16a**), mp 150–152° (reported[29] mp 150–151°), λ_{max}^{MeOH} 265 mμ (ε 9400), 205 (9000).

Anal. Calcd for $C_{10}H_{12}N_2O_3Cl_2$ (279.13): C, 43.03; H, 4.33; N, 10.04. Found: C, 43.16; H, 4.32; N, 10.19.

Elution of the major, slower band gave 1.4 g (63%) of 1-(3,5-dichloro-2,3,5-trideoxy-3-D-*threo*-pentofuranosyl)thymine (**17a**), mp 144–145° from chloroform–hexane, λ_{max}^{MeOH} 267 mμ (ε 9700), 210 (9300).

Anal. Calcd for $C_{10}H_{12}N_2O_3Cl_2$ (279.12): C, 43.03; H, 4.33; N, 10.03; Cl, 25.40. Found: C, 43.20; H, 4.44; N, 10.10; Cl, 25.28.

Bromination of Thymidine.—A solution of thymidine (1.94 g, 8 mmol), triphenylphosphine (6.30 g, 24 mmol), and CBr_4 (8.00 g, 24 mmol) in DMF (20 ml) was kept at room temperature for 7 days, diluted with methanol, and evaporated to dryness. Addition of ethyl acetate to the residue led to immediate separation of 1.96 g of crystalline **19** (see below). The filtrate was evaporated and applied to a column containing 1 kg of silicic acid. Elution with chloroform and then chloroform–ethyl acetate (9:1 and then 3:1) removed triphenylphosphine oxide with the later fractions also containing a thymidine derivative. These fractions were evaporated, dissolved in ethyl acetate, filtered to remove further phosphine oxide, and purified by preparative tlc using carbon tetrachloride–acetone (2:1) Elution of the major band gave 350 mg (12%) of 3′,5′-dibromo-3′,5′-dideoxythymidine (**16b**), mp 158–159° from chloroform–hexane (reported[30] mp 159°), λ_{max}^{MeOH} 266 mμ (ε 9800).

Further elution of the column with chloroform–ethyl acetate (3:1) gave 102 mg (4%) of pure 1-(3,5-dibromo-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)thymine (**17b**), mp 146–147° from chloroform–hexane, λ_{max}^{MeOH} 265 mμ (ε 9800), 206 (10,400).

Anal. Calcd for $C_{10}H_{12}N_2O_3Br_2$ (368.05): C, 32.63; H, 3.29; N, 7.61. Found: C, 33.08; H, 3.29; N, 7.42.

Continued elution of the column with acetone gave 1.42 g (60%) of crystalline 5′-bromo-5′-deoxythymidine (**18a**), mp 157–158° dec from methanol–ethyl acetate (reported[30] mp 154 and 129°), λ_{max}^{MeOH} 266 mμ (ε 9800), 207 (10,200).

Anal. Calcd for $C_{10}H_{13}N_2O_4Br$ (305.14): C, 39.36; H, 4.29; N, 9.18; Br, 26.19. Found: C, 39.47; H, 4.42; N, 9.38; Br, 26.16.

Acetylation of **18a** using acetic anhydride in pyridine–DMF gave the 3′-*O*-acetyl derivative (**18b**), mp 158.5–159.5° from chloroform–hexane. The nmr spectrum showed a downfield shift of 0.63 ppm for $C_{3'}H$ relative to **18a** while the other sugar protons remained essentially unchanged.

Anal. Calcd for $C_{12}H_{15}N_2O_5Br$: C, 41.51; H, 4.36; N, 8.07 Found: C, 41.21; H, 4.56; N, 7.95.

***N,N,N′,N′*-Tetramethylacrylamidinium Bromide (19).**—The crystalline material (1.96 g, 22%) which separated from the bromination of thymidine above was recrystallized from acetone–methanol, mp 163–164°, and shown to be a 2:1 complex of **19** and carbon tetrabromide. It moved as a monocharged cation on electrophoresis at pH 7.5. The presence of free CBr_4 was confirmed by quantitative glc using a column of 3% OVI on Gas-Chrom Q[49] at 90° and by the mass spectrum of **19**, which was identical with that of CBr_4: λ_{max}^{MeOH} 310 mμ (ε 33,900), 218 (4800); nmr (DMSO-d_6) 3.08 and 3.26 (s, 6, NMe_2), 5.43 (t, 1, J = 11 Hz, $CH{=}CH_2$), 7.79 ppm (d, 2, J = 11 Hz, $CH{=}CH_2$).

Anal. Calcd for $C_7H_{15}N_2Br \cdot {}^1/_2CBr_4$: C, 24.15; H, 4.05; N, 7.51; Br, 64.28. Found: C, 24.09; H, 4.04; N, 8.23; Br, 63.99.

***N,N,N′,N′*-Tetramethyl-2-bromoacrylamidinium Bromide (20).** **A. Using a 1:1 Ratio.**—Addition of CBr_4 (8 g, 24 mmol) to a solution of triphenylphosphine (6.4 g, 24 mmol) in DMF (40 ml) led to an exothermic reaction and separation of a crystalline material. After 24 hr this material (600 mg) was collected and recrystallized from methanol, giving 330 mg of **20** as a 2:1 complex with carbon tetrabromide: mp 204–205°; λ_{max}^{MeOH} 325 mμ (ε 35,100), 218 (6000); nmr (DMSO-d_5) 3.34 and 3.50 (s, 6, NMe_2), 8.31 ppm (s, 2, $CBr{=}CH_2$).

Anal. Calcd for $C_7H_{14}N_2Br_2 \cdot {}^1/_2CBr_4$: C, 19.93; H, 3.12; N, 6.20. Found: C, 19.99; H, 3.16; N, 6.20.

Evaporation of the filtrates from above and crystallization from methanol–ethyl acetate gave 1.0 g of yellow crystals that contained several minor impurities upon electrophoretic examination at pH 7.5. Several recrystallizations from methanol gave pure **19** identical with that above. Crystallization from methanol–benzene of the evaporated mother liquors after removal of **19** gave 1.07 g of dimethylamine hydrobromide,[50] mp 130–135°, identical in every way with an authentic sample. Finally, the mother liquors were partitioned between water and benzene and the organic phase was crystallized to give 6.0 g of triphenylphosphine oxide, mp 155–156°.

B. Using a 2:1 Ratio.—Carbon tetrabromide (4 g, 12 mmol) was added to a solution of triphenylphosphine (6.4 g, 24 mmol) in 30 ml of DMF giving an exothermic reaction which turned brown. After storage for 4 hr at 5° and then at −18° for 48 hr the mixture was filtered under nitrogen and the solid was washed with ethyl acetate, giving 2.5 g of yellow crystals. This was

(48) Very recently a preparation of **14c** was described by G. Etzold, R. Hintsche, G. Kowollik, and P. Langen, *Tetrahedron*, **27**, 2463 (1971). The reported melting point of 171–172° is considerably lower than that we report above.

(49) Applied Science Laboratories, Inc., State College, Pa.

(50) Dimethylamine hydrobromide has recently been isolated during unsuccessful attempts to brominate adenosine derivatives with triphenylphosphine and bromine in DMF: S. G. Verenikina, E. G. Chauser, and A. M. Yurkevich, *Zh. Obshch. Khim.*, **4**, 1630 (1971).

dissolved in methanol to destroy any triphenylphosphine dibromide, evaporated, extracted into ethyl acetate, and crystallized from methanol–ethyl acetate, giving 1.0 g of **19** identical with that above.

5′-*O*-Acetyl-2′-chloro-2′-deoxyuridine (24b).—Triphenylphosphine (1.048 g, 4 mmol) was added in four portions after 2, 4, 6, and 24 hr to a solution of **24a** (572 mg, 2 mmol)[37] and CCl_4 (1 ml) in DMF (10 ml). After 72 hr the solvent was evaporated *in vacuo* and the residue was purified by preparative tlc using two developments with chloroform–methanol (93:7). The major nucleoside band was eluted and rechromatographed using CCl_4–acetone (1:1), giving 230 mg (38%) of **24b**, mp 137–138° from acetone, λ_{max}^{MeOH} 258 mμ (ε 9600).

Anal. Calcd for $C_{11}H_{13}N_2O_6Cl$ (304.7): C, 43.36; H, 4.30; N, 9.20. Found: C, 43.26; H, 4.26; N, 9.77.

Brief treatment of this compound with methanolic sodium methoxide gave 2′-chloro-2′-deoxyuridine (**24c**), mp 205–206° from methanol (reported[35a] mp 207–212° dec) and in all ways identical with an authentic sample prepared by an independent route.[35a]

Chlorination of Uridine.—A solution of uridine (488 mg, 2 mmol), triphenylphosphine (1.6 g, 6 mmol), and CCl_4 (1 ml, 10 mmol) in DMF (10 ml) was kept at 23° for 5 days, evaporated to dryness, and separated by preparative tlc using chloroform–methanol (9:1). Two bands moving slower than triphenylphosphine oxide were obtained. Elution of the faster band gave 380 mg (68%) of 2′,5′-dichloro-2′,5′-dideoxyuridine (**25**),[51] mp 159–161° from chloroform–hexane, λ_{max}^{MeOH} 258 mμ (ε 9800).

Anal. Calcd for $C_9H_{10}N_2O_4Cl_2$ (281.10): C, 38.45; H, 3.58; Cl, 25.22. Found: C, 38.42; H, 3.77; Cl, 25.33.

Elution of the slower band gave 90 mg (17%) of 5′-chloro-5′-deoxyuridine (**4e**), mp 173–175° from acetone (reported[9] mp 170–172°), λ_{max}^{MeOH} 260 mμ (ε 10,300).

Anal. Calcd for $C_9H_{11}N_2O_5Cl$ (262.66): C, 41.15; H, 4.22; N, 10.67. Found: C, 40.96; H, 4.29; N, 10.66.

The identical compounds were also obtained by hydrolysis of **2a** with 90% formic acid at 20° for 18 hr.

Chlorination of N^4-Benzoylcytidine (26a).—A solution of **26a** (694 mg, 2 mmol),[36] triphenylphosphine (1.57 g, 6 mmol), and CCl_4 (1 ml, 10 mmol) in DMF (15 ml) was kept at 23° for 24 hr. Further portions (262 mg each) of triphenylphosphine were added after 1, 2, and 3 days and after a total of 4 days the mixture was evaporated to dryness. The residue was stirred with benzene–ether (1:1) which dissolved most of the triphenylphosphine oxide, leaving 1.3 g of insoluble material which was separated into two bands by preparative tlc using chloroform–methanol (9:1). Elution of the faster band gave 314 mg (41%) of N^4-benzoyl-2′,5′-dichloro-2′,5′-dideoxycytidine (**26c**), mp 165.5–167.5° from methanol, λ_{max}^{MeOH} 261 mμ (ε 25,200), 303 (10,200).

Anal. Calcd for $C_{16}H_{15}N_3O_4Cl_2$ (384.25): C, 50.01; H, 3.95; N, 10.93. Found: C, 49.51; H, 3.94; N, 10.88.

Elution of the slower band gave 220 mg (30%) of N^4-benzoyl-5′-deoxycytidine (**26b**), mp 216–218° from methanol, λ_{max}^{MeOH} 260 mμ (ε 24,300), 304 (ε 10,500)

Anal. Calcd for $C_{16}H_{16}N_3O_5Cl$ (365.77): C, 52.53; H, 4.41; N, 11.48. Found: C, 52.44; H, 4.35; N, 11.61.

3′-*O*-Acetyl-N^4-benzoyl-2′,5′-dichloro-2′,5′-dideoxycytidine (26d).—A solution of **26c** (38 mg, 0.1 mmol), acetic anhydride (0.3 ml), and pyridine (0.03 ml) in DMF (0.3 ml) was kept at 23° for 2 hr, evaporated to dryness, and coevaporated three times with toluene. Two crystallizations from acetone–hexane gave 28 mg (65%) of **26d**, mp 192–193°, λ_{max}^{MeOH} 261 mμ (ε 26,100), 301 (9600).

Anal. Calcd for $C_{18}H_{17}N_3O_5Cl_2$ (426.29): C, 50.71; H, 4.01; N, 9.85. Found: C, 50.85; H, 4.18; N, 9.54.

3-*O*-Formyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (27b).—Triphenylphosphine (655 mg, 2.5 mmol) was added portionwise over 48 hr to a solution of **27a** (269 mg, 1 mmol) and CCl_4 (1 ml) in DMF (5 ml) at which point tlc using CCl_4–acetone (9:1) showed the reaction to be complete. Evaporation of the solvent and preparative tlc was accompanied by considerable degradation. A relatively pure fraction (110 mg, 38%) of **27b** was, however, isolated and shown to be identical with an authentic sample prepared as below by tlc, nmr, and ir spectra.

An authentic sample of **27b** was prepared by treating **27a** (260 mg, 1 mmol) with formic acid (0.2 ml) and acetic anhydride (0.4 ml in pyridine (10 ml) for 4 days at −18°. After careful evaporation of the solvent, the residue was distilled in a short-path apparatus, bp 100° (10^{-3} mm): ν_{max} (neat) 1740 cm^{-1}; nmr ($CDCl_3$) 1.29 (s, 6, CMe_2), 1.39 and 1.50 (s, 3, CMe_2), 4.07 (m, 2, C_6H_2), 4.20 (m, 2, C_4H and C_5H), 4.53 (d, 1, $J_{1,2}$ = 4 Hz, C_2H), 5.35 (br s, 1, C_3H), 5.87 (d, 1, $J_{1,2}$ = 4 Hz, C_1H), 8.10 ppm (s, 1, OCHO).

Anal. Calcd for $C_{13}H_{20}O_7$ (288.29): C, 54.16; H, 6.99. Found: C, 53.84; H, 7.20.

Reaction of Uridine with Arsenic Trichloride in Dimethylacetamide.—Freshly distilled arsenic trichloride (1.86 g, 10.3 mmol, stored over AW-500 molecular sieve to remove traces of HCl) was added in a dry box to a solution of uridine (2.0 g, 8.2 mmol) in freshly dried (molecular sieve) and distilled dimethylacetamide (25 ml). The resulting solution was heated at 127° for 12 hr and then evaporated to dryness *in vacuo*. The residue was dissolved in water (pH <1), rapidly neutralized to pH 7 with ammonium hydroxide, and evaporated to dryness. The residue was extracted with methanol (10 ml), leaving a non-uv-absorbing residue. The extracts were evaporated to dryness and separated into three major bands (R_f's 0.57, 0.40, and 0.21) by preparative tlc using chloroform–methanol (9:1).[52] Elution of the fastest band gave 500–650 mg (four experiments) of material that was rechromatographed using either methylene chloride–acetone (55:45) or chloroform–methanol (4:1). Considerable degradation occurred during the two purifications, the major unchanged material (220 mg) being identified as 3′,5′-di-*O*-acetyl-2′-chloro-2′-deoxyuridine (**29**), which was identical with an authentic sample[44] by melting point (128–130°, reported mp 127–130°), nmr, and ir spectra. One of the degradation products was chromatographically identical with 5′-*O*-acetyl-2′-chloro-2′-deoxyuridine (**24b**), and in one experiment 2′-chloro-2′-deoxyuridine, mp 204–206°, was isolated in crystalline form and its structure confirmed by its nmr and ir spectra. The original middle band contained 150–250 mg of a mixture of 2′-chloro-2′-deoxyuridine (**24c**) and its 3′-*O*- and 5′-*O*-monoacetyl derivatives. Elution of the slowest band gave 1.4–1.5 g of a syrup that was rechromatographed on two plates using chloroform–methanol (4:1). The faster band contained 1 g (43%) of 5′-*O*-acetyluridine, which was crystallized from methanol giving 800 mg of **24a**, mp 163–163.5°, identical in every way with an authentic sample.[37] The mother liquor contained some 5′-chloro-5′-deoxyuridine (**4e**). The slower band gave 500 mg (25%) of unreacted uridine.

Registry No.—**2a**, 19556-51-5; **2b**, 19556-52-6; **2c**, 14671-65-9; **4b**, 34627-49-1; **4d**, 19556-55-9; **4e**, 19556-54-8; **5b**, 21017-03-8; **5c**, 31698-26-7; **6b**, 34627-54-8; **7a**, 34627-55-9; **7b**, 892-48-8; **8a**, 34627-57-1; **8b**, 34627-58-2; **9b**, 34627-59-3; **9c**, 31652-78-5; **10b**, 34627-61-7; **14a**, 14260-81-2; **14b**, 34627-62-8; **14c**, 25526-94-7; **15a**, 34627-64-0; **15b**, 34627-65-1; **16a**, 14260-86-7; **16b**, 34627-67-3; **17a**, 34627-68-4; **17b**, 34627-69-5; **18a**, 25905-51-5; **18b**, 34647-05-7; **18c**, 25905-50-4; **19**, 34627-43-4; **20**, 34627-44-6; **24b**, 34627-72-0; **25**, 34627-73-1; **26b**, 34627-74-2; **26c**, 34627-75-3; **26d**, 34627-76-4; **27b**, 34627-77-5; triphenylphosphine oxide, 791-28-6.

(51) The configuration at $C_{2'}$ of **25** was confirmed by preparation of the identical compound *via* reaction of **24c** (131 mg, 0.5 mmol) with triphenylphosphine (140 mg, 0.25 mmol) and CCl_4 (0.11 ml, 1.1 mmol) in DMF (1.5 ml) for 16 hr. Preparative tlc and crystallization from chloroform gave 115 mg (82%) of **25** identical with that above.

(52) The relative positions of the bands was similar to that obtained using 1-butanol–water (86:14)[9] but the resolution was better.

Purine Nucleosides. XXXI. The Directive Effect Which Certain Exocyclic Substituents at C-8 of Adenine Have on the Site of Ribosylation[1]

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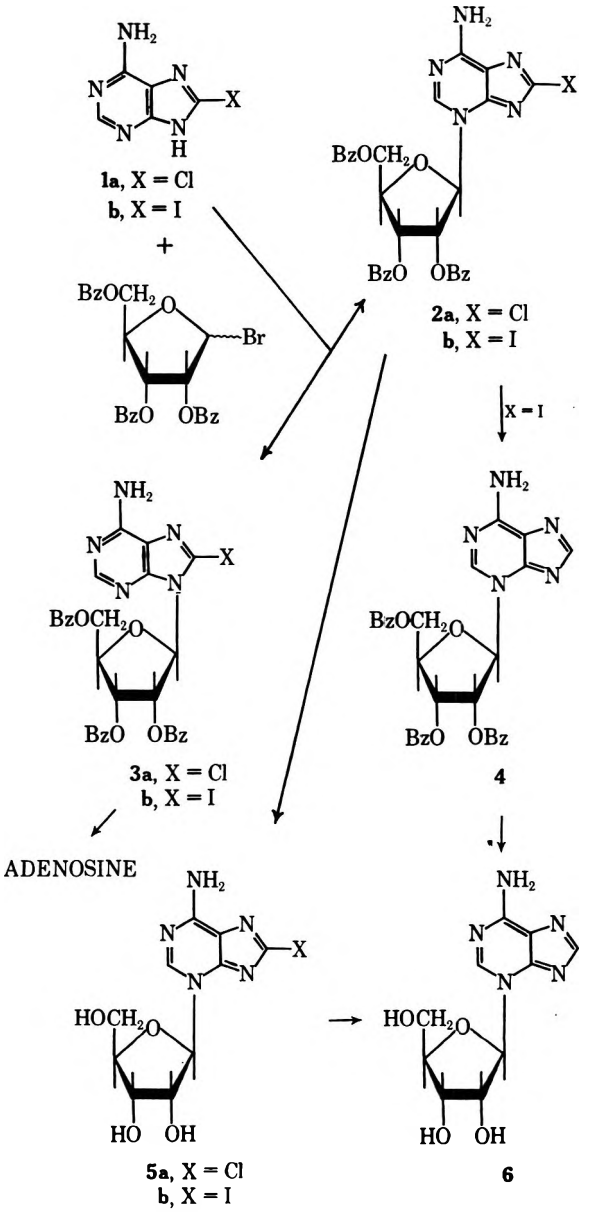
The extent to which different exocyclic substituents at the 8 position of adenine (H, Cl, I) influences the ratio of 3-ribosidation to 9-ribosidation has been studied. It has been established that the ratio can be correlated directly to the size of the group residing at the 8 position which indicates that steric considerations are probably the predominant factor.

It has been reported[2-5] that adenine is preferentially alkylated in the 3 position to yield predominantly 3-methyladenine. However, it has also been reported[6] that the "alkylation" of adenine with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in acetonitrile furnished two isomers [3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)adenine (25%) and 9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)adenine (18%)]. It was proposed[6] that the bromo sugar was so reactive that the directive forces were less important, which accounted for the lack of specificity. An examination of space-filling molecular models (CPK) indicated that the insertion of a bulky group at C-8 of adenine would provide considerable steric hindrance to a large group attempting to enter at the 9 position. This prompted the present investigation in an effort to determine whether a steric effect would be observed in the ribosylation of 8-chloro- and 8-iodoadenine and if the effect could be correlated to the size of the 8 substituent.

8-Chloroadenine (**1a**) was stirred for 3 days with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in dimethylformamide at 50° to provide starting material (**1a**, 32%) and two additional products, one a crystalline material (mp 231–232°) (22%) and the second a foam (12.5%). The pmr spectra of these compounds showed the H_2 signal to be at δ 8.68 and 8.99, respectively, as compared to δ 8.30 for 8-chloroadenine, *per se*. These spectra also showed all the characteristic peaks of a carbohydrate moiety in the proper proportion for a 1:1 adduct of carbohydrate to heterocyclic aglycon. Therefore, these two products were identified as nucleosides[7] of **1a** and on the basis of the work cited earlier they were tentatively assigned as the N-3 and N-9 isomers (**2a** and **3a**). The crystalline material, on treatment with methanolic ammonia, gave a product which was tentatively assigned as **5a** (mp 205° dec). The pmr spectrum of **5a** showed a singlet at δ 8.62 (H_2) and a doublet at 5.93 ($H_{1'}$). Dehalogenation with 10% palladium on charcoal and H_2 gas gave a good yield of nucleoside material (mp 213–215°). A comparison of the ultraviolet spectra of this nucleoside with that previously reported[6] for 3-β-D-ribofuranosyladenine (**6**) showed them to be identical and established



the structure of **2a** as 8-chloro-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)adenine and **5a** as 8-chloro-3-(β-D-ribofuranosyl)adenine. The pmr spectrum of **6** showed two singlets at δ 7.80 and 8.59. Comparing this spectrum with that of **5a** (singlet at δ 8.62) allowed us to unequivocally assign the downfield signal to H_2 and the signal at δ 7.80 to H_8. Treatment of the second product (**3a**) with methanolic ammonia, followed by 10% palladium on charcoal and H_2 gas, gave adenosine, as shown by a comparison of ultraviolet spectra and thin layer chromatographic properties with an authentic

(1) This work has been supported by Research Grant No. CA-11147, National Cancer Institute, National Institutes of Health, Public Health Service.

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(3) N. J. Leonard and J. A. Deyrup, *ibid.*, **84**, 2148 (1962).

(4) N. J. Leonard and T. Fujii, *ibid.*, **85**, 3719 (1963), and references cited therein.

(5) B. C. Pal, *Biochemistry*, **1**, 558 (1962).

(6) N. J. Leonard and R. A. Laursen, *ibid.*, **4**, 354 (1965).

(7) L. B. Townsend in "Synthetic Procedures in Nucleic Acid Chemistry," Vol. II, W. Werner Zorbach and R. Stuart Tipson, Ed., Interscience, New York, N. Y., 1972.

sample of adenosine. Thus, the structure of **3a** was established as 8-chloro-9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)adenine. Further corroboration for these assignments was obtained by application of the Δδ rule.[8] Attempts to dehalogenate **2a** and **3a** directly were unsuccessful, presumably because of their insolubility in the solvents suitable for the reaction.

In an effort to increase the yield of the 3 isomer, we increased the size of the 8 substituent of adenine. 8-Iodoadenine was stirred with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in dimethylformamide for 3 days at 50° to yield recovered 8-iodoadenine (**1b**, 31%) and two other products which by analogy to the reaction of 8-chloroadenine were tentatively assigned to be 8-iodo-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-adenine (**2b**, 30%) and 8-iodo-9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)adenine (**3b**, 5.5%). In this case, **2b** was dehalogenated using 5% palladium on charcoal and H_2 gas to yield 3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)adenine (**4**). Removal of the blocking groups from the carbohydrate moiety with methanolic ammonia furnished 3-(β-D-ribofuranosyl)adenine (**6**). The above structure assignments were corroborated when the ultraviolet spectra and melting points of both nucleosides (**4** and **6**) agreed with those previously reported.[6] The structure of 8-iodo-tri-*O*-benzoyladenosine was established by dehalogenation with palladium on charcoal and H_2 gas to afford the previously reported 9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)adenine[6] and debenzoylation with methanolic ammonia to furnish adenosine (as established by ultraviolet spectra and tlc).

Therefore, the above data indicate that a substituent at position 8 of adenine has a marked influence on the site of ribosidation. The possibility that this influence is partially electronic cannot be discounted. However, if the primary electronic effect of the 8 substituent is inductive, one would expect 8-chloroadenine with the more electronegative chloro group (electronegativity 3.0) to give a higher ratio N-3 substitution to N-9 substitution than either 8-iodoadenine or adenine (electronegativities of H and I, 2.1 and 2.5, respectively). This would be due to a decrease in electron density in the imidazole ring relative to the pyrimidine ring. This is not the case, since the observed N-3:N-9 ratios for 8-iodo, 8-chloro, and 8-hydrogen are 5.5, 1.8, and 1.4, respectively. For an electronic rationale to be invoked would require that the resonance contribution by the 8-chloro group be of sufficient magnitude to more than compensate for the difference in electronegativity. On the other hand, an examination of space-filling molecular models (CPK) indicates that steric hindrance to attack at N-9 would result from the close proximity of a bulky 8 substituent and the large benzoyl group on the 2 position of the entering carbohydrate, while no such hindrance would be present for N-3 attack. This suggests that steric factors play the predominant role in determining the isomer ratios in these reactions.

Experimental Section

Melting points were determined with a Thomas–Hoover melting point apparatus and are uncorrected. Proton magnetic resonance spectra were measured with a Varian A-60 nmr spectrometer using tetramethylsilane as an internal standard. Ultraviolet spectra were determined with a Beckman DK-2 spectrophotometer and thin layer chromatography was run on SilicAR 7GF (Mallinckrodt). Elemental analyses were performed by Heterocyclic Chemical Corp., Harrisonville, Mo.

2,3,5-Tri-*O*-benzoyl-D-ribofuranosyl bromide was prepared by adding 20 ml of dichloromethane previously saturated at −30° with hydrogen bromide to a CH_2Cl_2 solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (2.7 g) also cooled to −30°. The solution was allowed to warm up to 0° and then evaporated to dryness *in vacuo*. The remaining traces of hydrogen bromide and acetic acid were removed by coevaporation with cold toluene (0°). The resulting syrup was used in the following reactions without further purification.

8-Chloro-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)adenine (2a) and 8-Chloro-9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)adenine (3a).—To 8-chloroadenine[9] (1.0 g, 5.9 mmol) was added 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide prepared from 3.0 g (5.95 mmol) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose and a catalytic amount of potassium iodide (2–5 mg) in 25 ml of dry dimethylformamide (AR grade, dried over 5 Å molecular sieves). The mixture was protected from moisture, stirred at 50° for 3 days, and then added dropwise with stirring to a mixture of ammonium hydroxide (28%) (1.5 ml) and water (400 ml). The solid was collected by filtration (3.5 g), dissolved in methanol (150 ml), and allowed to stand at room temperature for 16 hr. 8-Chloro-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)adenine (**2a**, 0.6 g) was collected by filtration and the methanol filtrate was evaporated to a volume of 15 ml and applied to three SilicAR 7GF preparative thick layer chromatography plates (20 × 40 cm, 3 mm thick). The plates were developed with a chloroform–acetone (4:1) mixture, the two uv-absorbing bands [**2a**, R_f 0.36 and 8-chloro-9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)adenine (**3a**, R_f 0.56)] were removed and each nucleoside was eluted with hot methanol (50 ml). The fraction containing **2a** was evaporated to 10 ml on standing at room temperature to yield an additional 0.1 g of crystalline **2a** for a total yield of **2a** of 0.79 g (21%): mp 231–232°; uv λ_{max}, nm (ε × 10^{-3}), pH 1, 281 (24.5), 230.5 (51.5); pH 11, sh 318 (17.5), 306 (19.9), sh 285 (18.7), sh 279 (18.1), 237 (39.8); EtOH, sh 292 (16.2), 282.5 (17.5), sh 277 (16.2), 229 (54.0).

Anal. Calcd for $C_{31}H_{24}ClN_5O_7$ (**2a**): C, 60.84; H, 3.95; N, 11.40. Found: C, 60.82; H, 4.07; N, 11.18.

Evaporation *in vacuo* of the second methanol fraction yielded 0.45 g (12.5%) of **3a** as a foam, uv λ_{max}, nm (ε × 10^{-3}), pH 1, 261 (18.7), 233 (41.3).

Anal. Calcd for $C_{31}H_{24}ClN_5O_7 \cdot {}^1/_2H_2O$ (**3a**): C, 59.95; H, 4.06; N, 11.28. Found: C, 59.98; H, 4.10; N, 11.21.

Acidification (pH 4) of the aqueous filtrate from above resulted in the precipitation of unreacted 8-chloroadenine (**1a**, 0.32 g).

8-Iodo-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)adenine (2b) and 8-Iodo-9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)adenine (3b).—2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl bromide, prepared from 1.9 g (3.8 mmol) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, and a catalytic amount of potassium iodide (2–5 mg) in dry dimethylformamide (25 ml) were added to 8-iodoadenine[10] (**1b**, 1.0 g, 3.8 mmol). The mixture was stirred at 50° for 3 days and the nucleosides (**2b**, R_f 0.69 and **3b**, R_f 0.78) were isolated as described above to yield 0.8 g (30%) of 8-iodo-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)adenine (**2b**): mp 233–234°; uv λ_{max}, nm (ε × 10^{-3}), pH 1, sh 296 (21.2), 288 (24.0), 232 (52.2); pH 11, sh 326 (18.4), 315 (19.8), 238.5 (36.0); EtOH, 298.5 (18.4), sh 286 (16.6), 230 (56.5).

Anal. Calcd for $C_{31}H_{24}IN_5O_7$ (**2b**): C, 52.77; H, 3.43; N, 9.97. Found: C, 52.39; H, 3.44; N, 9.76.

The yield of 8-iodo-9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-adenine (**3b**) was 0.015 g (5.5%) (syrup): uv λ_{max}, nm (ε × 10^{-3}), pH 1, 262.5 (24.7), 233 (52.9).

Anal. Calcd for $C_{31}H_{24}IN_5O_7$ (**3b**): N, 9.97. Found: N, 9.70.

The yield of recovered 8-iodoadenine (**1b**) was 0.31 g (31%).

3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)adenine (4).—8-Iodo-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)adenine (**2b**, 1.0 g) was suspended in a mixture of ethyl acetate (60 ml) and ethanol (40 ml). Sodium acetate (0.2 g) and 5% palladium on charcoal (0.5 g) were then added and the suspension was shaken on a

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Parr hydrogenation apparatus under 40 psi of hydrogen gas at room temperature for 22 hr. The mixture was filtered through a celite bed and the filtrate was boiled down to a volume of 50 ml. The solution was allowed to stand at room temperature overnight to yield 0.44 g of **4**: mp 242–244° dec (reported[6] mp 246–247°); mixture melting point with an authentic sample[6] showed no depression; uv λ_{max}, nm ($\epsilon \times 10^{-3}$), pH 1, 276 (24.3), 230.5 (48.4); pH 11, sh 318 (14.8), 304 (17.4), 285 (18.0), 235 (37.4); EtOH, sh 294 (12.7), 279 (16.0), 229.5 (51.9).

Anal. Calcd for $C_{31}H_{25}N_5O_7$: C, 64.23; H, 4.34; N, 12.08. Found: C, 64.25; H, 4.24; N, 12.17.

3-(β-D-Ribofuranosyl)adenine (6). Method 1.—3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)adenine (**4**, 0.18 g) was suspended in 15 ml of methanol, previously saturated at −5° with ammonia, in a sealed flask and allowed to stand at room temperature for 3 days. The resulting solution was evaporated to dryness *in vacuo* and the residue was extracted with ethyl ether (3 × 25 ml) leaving 0.08 g of solid. Recrystallization of this solid from a methanol–water mixture (about 3:1) furnished an analytical sample of **6**: mp 213–215° (reported[6] mp 210–211°); uv λ_{max}, nm ($\epsilon \times 10^{-3}$), pH 1, 274 (21.1); pH 11, 277 (15.0).

Anal. Calcd for $C_{10}H_{13}N_5O_4$: C, 44.91; H, 4.90; N, 26.19. Found: C, 44.89; H, 4.82; N, 26.12.

Method 2.—8-Chloro-3-(β-D-ribofuranosyl)adenine (**5a**, 0.1 g) was dissolved in water (5 ml) and then sodium acetate (0.1 g) and 10% palladium on charcoal (0.05 g) were added. The suspension was shaken on a Parr hydrogenation apparatus under 40 psi of hydrogen gas for 48 hr at room temperature and filtered through a celite bed, and the catalyst was washed with hot water (2.0 ml). The filtrate was evaporated to dryness *in vacuo* and the residue was recrystallized from methanol–water (5:1) to yield 0.04 g of product. Ultraviolet spectra and thin layer chromatography showed the product to be identical in all respects with that obtained by method 1, and a mixture melting point showed no depression.

8-Chloro-3-(β-D-ribofuranosyl)adenine (5a).—8-Chloro-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)adenine (**2a**, 0.25 g) was suspended in 50 ml of methanol, previously saturated at −5° with ammonia, in a sealed flask and then allowed to stand at room temperature for 4 days. The resulting solution was evaporated to dryness *in vacuo* and the residue was extracted with ethyl ether (3 × 25 ml). The remaining solid was dissolved in ethanol. The solution was cooled to 0° and the crystals which had formed after 18 hr were collected by filtration and washed with ethanol (2 ml) to yield 0.09 g of product which decomposes slowly above 205°; uv λ_{max}, nm ($\epsilon \times 10^{-3}$), pH 1, 279 (22.0); pH 11, 283 (17.8).

Anal. Calcd for $C_{10}H_{12}ClN_5O_4$: C, 39.79; H, 4.27; N, 23.15. Found: C, 39.52; H, 4.25; N, 22.93.

8-Iodo-3-(β-D-ribofuranosyl)adenine (5b).—8-Iodo-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)adenine (**2b**) (0.7 g) was suspended in methanol, saturated with ammonia at −5° (50 ml), in a sealed flask, and allowed to stand at room temperature for 4 days. The solution was evaporated to dryness *in vacuo* and the residue was extracted with ethyl ether (4 × 25 ml). The solid which remained was recrystallized from ethanol to yield 0.27 g of product: mp 202–205° dec; uv λ_{max}, nm ($\epsilon \times 10^{-3}$), pH 1, sh 295 (24.0), 287 (28.6), sh 227 (29.4); pH 11, 292.5 (19.1) 230 (15.9).

Anal. Calcd for $C_{10}H_{12}IN_5O_4$: C, 30.55; H, 3.08; N, 17.82. Found: C, 30.48; H, 3.21; N, 17.51.

8-Chloro-9-(β-D-ribofuranosyl)adenine.—8-Chloro-9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)adenine (**3a**, 0.3 g) was added to methanol saturated with ammonia (saturated at −5°) (25 ml) in a sealed flask and allowed to stand for 4 days at room temperature. The solution was evaporated to dryness and the resulting syrup was extracted with ethyl ether (4 × 25 ml) to yield a solid. This solid was dissolved in ethanol and applied to a SilicAR 7GF thick layer plate (20 × 40 cm, 3 mm thick) and developed with ethyl acetate–ethanol (4:1). The band at R_f 0.53 was eluted with hot methanol (50 ml) and the eluent was allowed to evaporate to 25 ml on standing to yield 0.06 g of product: mp 209–211° (cloudy melt); uv λ_{max}, nm ($\epsilon \times 10^{-3}$), pH 1, 260 (19.3); H_2O, 262 (18.7); pH 11, 262 (19.8).

Anal. Calcd for $C_{10}H_{12}ClN_5O_4 \cdot {}^1/_2H_2O$: C, 38.56; H, 4.20; N, 22.48. Found: C, 38.85; H, 4.12; N, 22.53.

Adenosine. Method 1.—8-Chloro-9-(β-D-ribofuranosyl)-adenine (0.035 g) was dissolved in water (5 ml) containing sodium acetate (0.05 g), 10% palladium on charcoal (0.02 g) was added, and the suspension was shaken under 40 psi of hydrogen gas on a Parr hydrogenation apparatus for 40 hr. The mixture was filtered, the palladium on charcoal was washed with boiling water (5 ml), and the filtrate was evaporated to 3 ml on standing at room temperature to yield crystals (6 mg). A comparison of ultraviolet spectra and thin layer chromatographic properties with those of an authentic sample of adenosine showed them to be identical.

Method 2.—8-Iodo-9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-adenine (**3b**, 0.010 g) was dissolved in a mixture of ethyl acetate (3 ml) and ethanol (2 ml) containing sodium acetate (5 mg), and 10% palladium on charcoal (8 mg) was added. The suspension was shaken under 40 psi of hydrogen as on a Parr hydrogenation apparatus for 24 hr and then filtered, and the catalyst was washed with boiling ethyl acetate. The filtrate was evaporated to dryness *in vacuo* and the solid residue was suspended in methanol saturated at −5° with ammonia and allowed to stand at room temperature for 3 days. The solution was evaporated to dryness. The residue was extracted with ethyl ether (4 × 10 ml) and the solid which remained was dissolved in hot water (2 ml) and allowed to stand at room temperature overnight to yield a small amount of crystalline product (yield not determined). Comparison of ultraviolet spectra and thin layer chromatographic properties with an authentic sample of adenosine showed this product to be identical with adenosine.

Registry No.—**2a**, 34388-76-6; **2b**, 34402-59-0; **3a**, 34388-77-7; **3b**, 34408-09-8; **4**, 28837-63-0; **5a**, 34408-11-2; **5b**, 34408-12-3; **6**, 2273-78-1; 8-chloro-9-(β-D-ribofuranosyl)adenine, 34408-14-5.

Cholecystokinin–Pancreozymin. I. The Synthesis of Peptides Corresponding to the N-Terminal Sequence[1]

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The preparation of a protected octapeptide, bis-*tert*-butyloxycarbonyl-L-lysyl-L-alanyl-L-prolyl-L-serylglycyl-L-arginyl-L-valyl-L-serine hydrazide (XVIII), is described. The synthesis of a hexapeptide, L-lysyl-L-alanyl-L-prolyl-L-serylglycyl-L-arginine (X), identical with the N-terminal tryptic peptide of cholecystokinin–pancreozymin, is also reported.

The sequence of the 33 amino acids which constitute the single chain of the intestinal hormone cholecystokinin–pancreozymin (CCK) has been revealed by the investigations of Jorpes and Mutt.[2,3] A dodecapeptide identical with the C-terminal tryptic peptide of the hormone has been synthesized by Ondetti and his coworkers,[4] as well as several analogs of that sequence.[5] Because of the problems anticipated in working in a stepwise manner[6] with peptides containing an L-tyrosine-*O*-sulfate residue, a fragment condensation strategy seemed to be advisable for the total synthesis of the hormone. The preparation of a protected octapeptide, bis-*tert*-butyloxycarbonyl-L-lysyl-L-alanyl-L-prolyl-L-serylglycyl-L-arginyl-L-valyl-L-serine hydrazide (XVIII), which corresponds to the 1–8 sequence of the hormone, is described. This derivative is expected to be applicable in the synthesis of the 1–16 sequence of the hormone, and eventually of the whole molecule or its analogs. This paper deals in part with the synthesis of a free hexapeptide, L-lysyl-L-alanyl-L-prolyl-L-serylglycyl-L-arginine, corresponding in sequence to the N-terminal tryptic peptide. The syntheses of these two peptides are represented in Charts I, II, and III.

The intermediate common in both syntheses, the pentapeptide derivative bis-*tert*-butyloxycarbonyl-L-lysyl-L-alanyl-L-prolyl-*O*-benzyl-L-serylglycine ethyl ester (VII), was prepared in a stepwise manner. *N-tert*-Butyloxycarbonyl-*O*-benzyl-L-serine and glycine ethyl ester hydrochloride were coupled with dicyclohexylcarbodiimide[7] in the presence of diisopropylethylamine.[8] The dipeptide I was deprotected with trifluoroacetic acid, and acylated with *N-tert*-butyloxycarbonyl-L-proline *p*-nitrophenyl ester.[9] The peptide chain was elongated by the similar application of active esters of *N-tert*-butyloxycarbonyl-L-alanine[10] and bis-*tert*-butyloxycarbonyl-L-lysine.[11]

For the synthesis of the N-terminal hexapeptide X, the pentapeptide ester VII was converted to the corresponding hydrazide VIII and, after treatment with nitrous acid, was coupled to L-nitroarginine benzyl ester.[12] The protected hexapeptide IX was deblocked in two stages (Chart I). The product X was shown to be chromatographically and electrophoretically indistinguishable from the peptide isolated from the tryptic digest of cholecystokinin–pancreozymin.[13]

Initially, synthesis of protected octapeptide hydrazide XVIII was attempted by coupling the pentapeptide azide prepared from VIII to L-nitroarginyl-L-valyl-*O*-benzyl-L-serine *p*-nitrobenzyloxycarbonyl hydrazide. Hydrogenation of the product gave a multicomponent mixture. A more successful approach to the synthesis of XVIII (Chart II) started with the coupling of *N*-benzyloxycarbonyl-L-valine to serine methyl ester with dicyclohexylcarbodiimide.[7] (Woodwards Reagent K[14] proved less satisfactory in this coupling reaction.) The protected dipeptide XI was hydrogenated in the presence of 1 equiv of hydrochloric acid, and the deprotected dipeptide XII was acylated with *N*-benzyloxycarbonyl-L-nitroarginine pentachlorophenyl ester.[15] The tripeptide XIII was readily purified by recrystallization and was hydrogenated, in the presence of 5 equiv of hydrochloric acid, to simultaneously remove the *N*-benzyloxycarbonyl and nitro groups, giving the tripeptide XIV as a dihydrochloride. The pentapeptide hydrazide XVI was best prepared by hydrogenation of peptide VII followed by treatment of the product with hydrazine, rather than by directly hydrogenating the pentapeptide hydrazide VIII. The coupling reaction of the azide formed from a slight excess of the hydrazide XVI with the tripeptide dihydrochloride XIV proceeded well, and the product, the octapeptide XVII, could be purified by chromatography on carboxymethylcellulose. This octapeptide ester was rapidly and smoothly converted into the desired hydrazide XVIII on treatment with excess hydrazine in methanol for 24 hr. Since the suitability of XVIII as an intermediate in the synthesis of CCK by fragment condensation remains somewhat uncertain, an alternative route, involving an active ester of the N-terminal pentapeptide, was also explored. The synthesis of this active ester, bis-*tert*-butyloxycarbonyl-L-lysyl-L-alanyl-L-prolyl-L-serylglycine pentachlorophenyl ester (XXVII), is summarized in Chart III, which also shows the coupling of XXVII to XIV, yielding XVIII.

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CHART I

SYNTHESIS OF THE HEXAPEPTIDE CCK_{1-6}

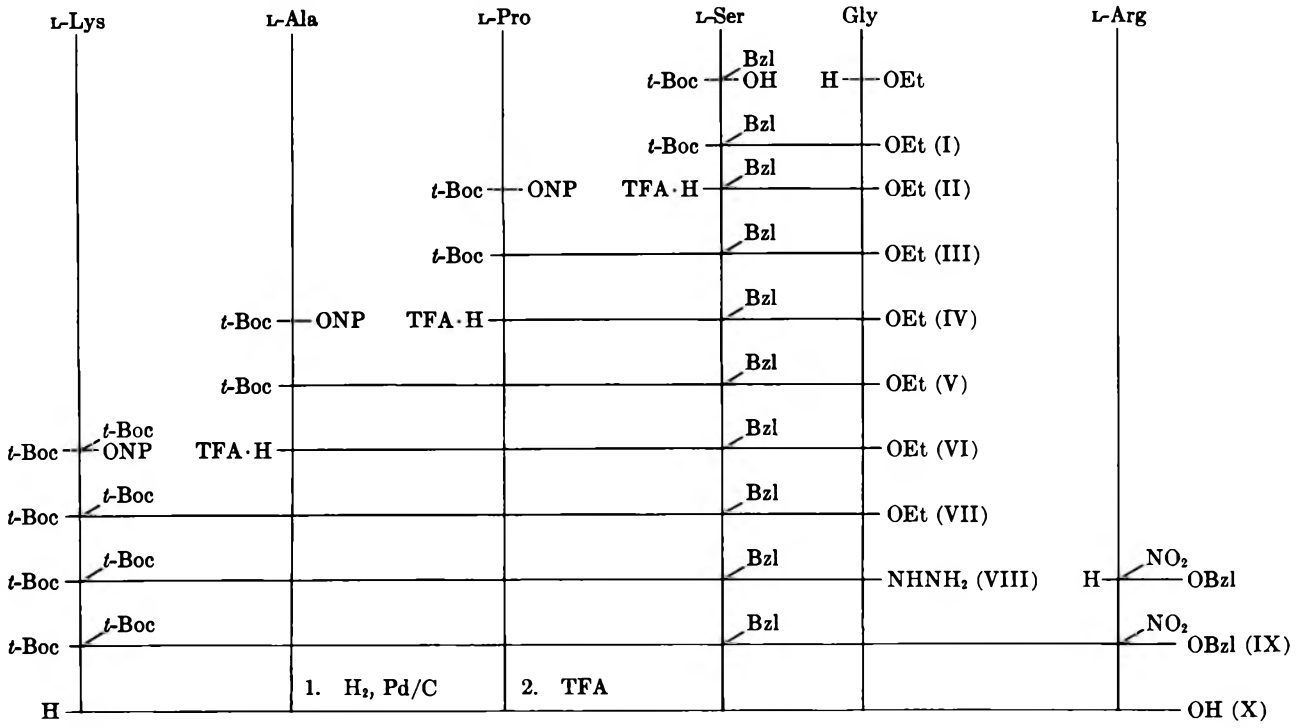
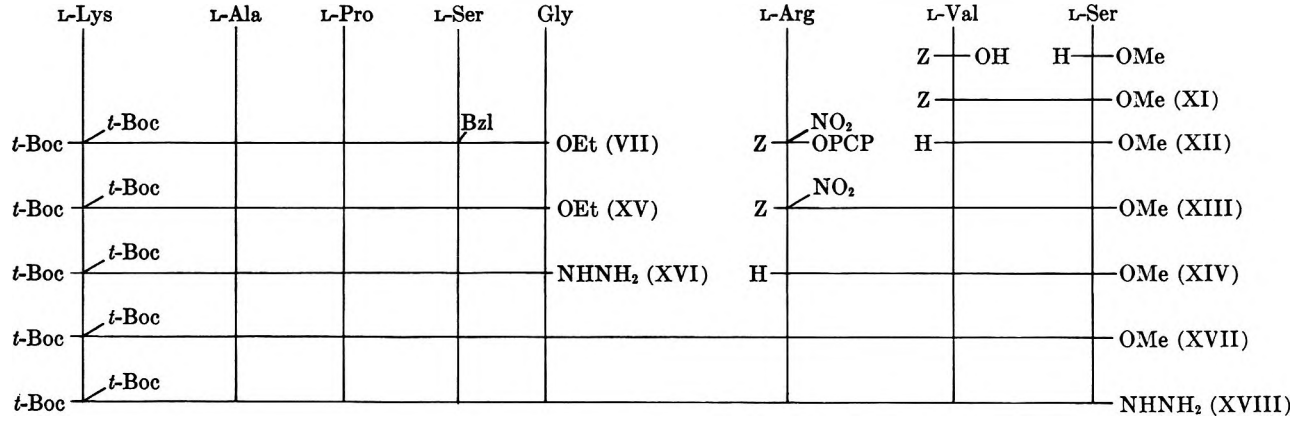


CHART II

AZIDE SYNTHESIS OF THE PROTECTED OCTAPEPTIDE (XVIII) HYDRAZIDE CORRESPONDING TO CCK_{1-6}



Experimental Section

Capillary melting points are reported uncorrected. For thin layer chromatography, the protected peptides were revealed by *tert*-butyl hypochlorite–KI–starch reagents,[16] or by the method of charring developed by Ziminski and Borowski.[17] The following solvent systems were used for development: A, *n*-BuOH–AcOH–H_2O (4:1:1); B, *n*-BuOH–AcOH–H_2O (3:1:1); C, *n*-BuOH–pyridine–AcOH–H_2O (30:20:6:24); D, EtOAc–pyridine–AcOH–H_2O (60:20:6:11); E, $CHCl_3$–MeOH (9:1); F, *n*-BuOH–AcOH–H_2O (4:1:5); G, *n*-PrOH–H_2O (7:3).

For amino acid analysis, samples were hydrolyzed with constant-boiling HCl in evacuated, sealed ampoules at 110° for 16 hr, and analyzed by the Spackman–Stein–Moore method[18] on a Beckman Spinco 120C amino acid analyzer.

N-tert-**Butyloxycarbonyl-*O*-benzyl-L-serylglycine Ethyl Ester (I).**—Glycine ethyl ester hydrochloride (2.8 g, 20 mmol), diisopropylethylamine[8] (2.60 g, 20 mmol), and *tert*-butyloxycarbonyl-*O*-benzyl-L-serine (2.96 g, 10 mmol) were dissolved in $CHCl_3$ (30 ml). The solution was stirred and cooled to 0°, and dicyclohexylcarbodiimide (DCC, 2.5 g, 12 mmol) was added. After stirring overnight at room temperature, the mixture was filtered and the filtrate was evaporated. The oily residue was dissolved in EtOAc, and a few drops of AcOH were added. After 1 hr, the precipitated *N,N'*-dicyclohexylurea (DCU) was removed by filtration and the filtrate was washed with cold 10% citric acid solution, H_2O, 5% $NaHCO_3$ solution, and H_2O, dried over $MgSO_4$, and evaporated *in vacuo*. The sirupy residue was dissolved in ether, from which crystals of the dipeptide appeared on standing. Recrystallization from ether gave 3.3 g (86%): mp 87–88°; $[\alpha]^{24}D$ +24.5° (*c* 3, DMF); tlc R_f A 0.70, R_f C 0.69; amino acid analysis, Ser, 1.0, Gly, 1.1.

Anal. Calcd for $C_{19}H_{28}N_2O_6$ (380.4): C, 60.0; H, 7.4; N, 7.4. Found: C, 60.2; H, 7.5; N, 7.3.

N-tert-**Butyloxycarbonyl-L-prolyl-*O*-benzyl-L-serylglycine Ethyl Ester (III).**—The protected dipeptide I (5 g, 13 mmol) was dissolved in trifluoroacetic acid (TFA, 50 ml). After 30 min at 15°, the TFA was evaporated *in vacuo* and the residue was triturated with ether, filtered, washed with ether, and dried to give 4.6 g (91%): mp 116–117°; tlc R_f A 0.55, R_f C 0.62.

The dipeptide trifluoroacetate II (4.3 g, 11 mmol), *tert*-butyloxycarbonyl-L-proline *p*-nitrophenyl ester[9] (4.0 g, 12 mmol), and triethylamine (TEA, 1.1 g, 11 mmol) were dissolved in CH_3CN (25 ml), and the solution was stirred overnight. The

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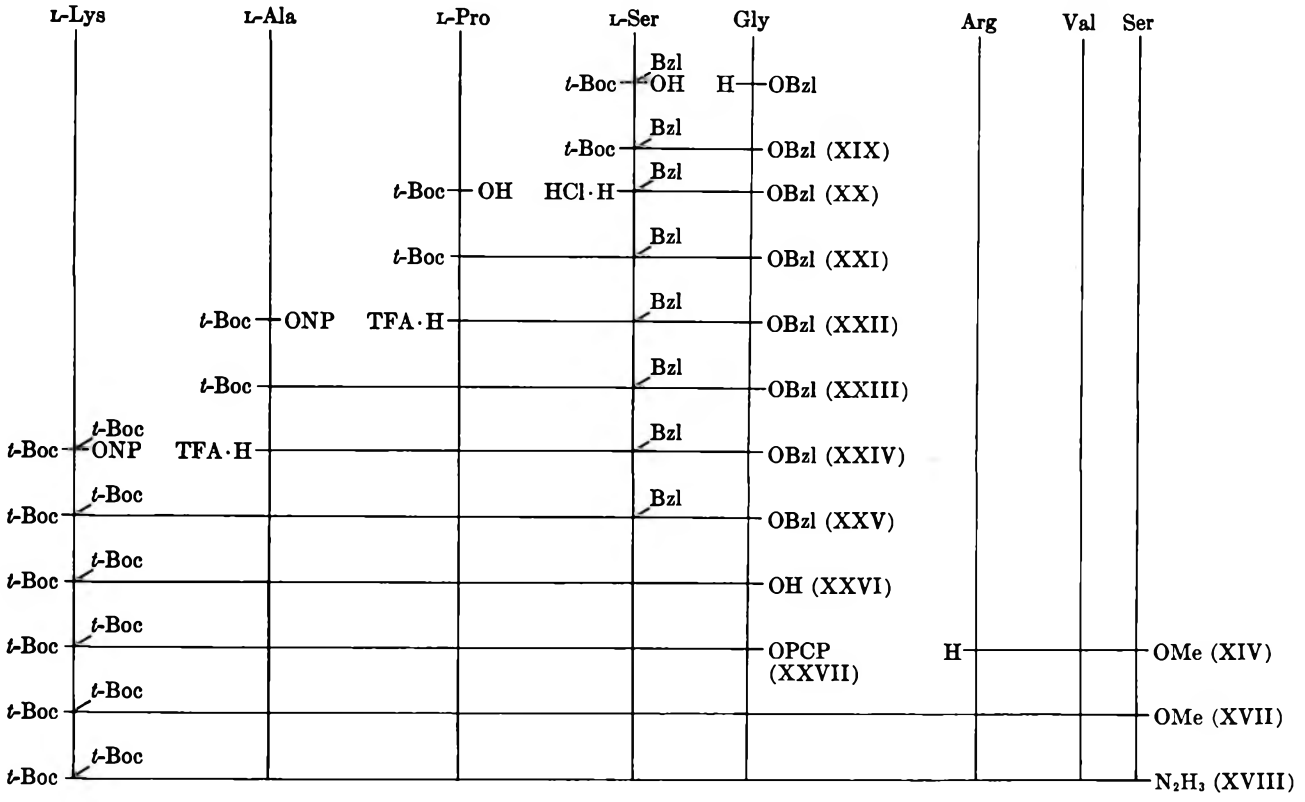
CHART III

ACTIVE ESTER SYNTHESIS OF XVIII



solvent was replaced with EtOAc, and the solution was washed with cold 10% citric acid solution, H_2O, and 0.75 *M* NH_4OH. The organic phase was dried over $MgSO_4$ and then evaporated to a sirupy residue which was dissolved in ether. On standing, crystals (1.3 g) separated. The mother liquors were treated with unsymmetrical dimethylethylenediamine[19] (0.88 g, 10 mmol) and, after 6 hr, the solution was washed with citric acid solution and dilute NH_4OH. On evaporation, an additional amount (2.5 g) of the pure tripeptide was obtained, giving a total yield of 3.8 g (60%): mp 109–110°; $[\alpha]^{24}D$ −9° (*c* 2.25, DMF); tlc R_f A 0.70, R_f C 0.69; amino acid analysis, Pro, 1.0, Ser, 0.8, Gly, 0.9.

Anal. Calcd for $C_{24}H_{35}N_3O_7$ (477.6): C, 60.4; H, 7.4; N, 8.8. Found: C, 60.5; H, 7.5; N, 9.0.

***N*-*tert*-Butyloxycarbonyl-L-alanyl-L-prolyl-*O*-benzyl-L-serylglycine Ethyl Ester (V).**—The tripeptide III (3.8 g, 8 mmol) was dissolved in TFA (40 ml). After 30 min at 20°, the TFA was evaporated *in vacuo*, and the residue was triturated with ether, washed with ether, and dried to give IV: 3.5 g (89%); mp 162–163°; paper chromatography R_f F 0.71, R_f C 0.77; tlc R_f A 0.44, R_f C 0.60.

The tripeptide trifluoroacetate IV (3.45 g, 7 mmol), TEA (0.7 g, 7 mmol), and *tert*-butyloxycarbonyl-L-alanine *p*-nitrophenyl ester[10] (2.5 g, 8 mmol) were dissolved in CH_3CN (30 ml). After the solution had been stirred overnight, the excess of *p*-nitrophenyl ester was decomposed with unsymmetrical dimethylethylenediamine.[19] The mixture was worked up as described for compound III to give 2.86 g (75%): mp 132–133°; $[\alpha]^{24}D$ −23.5° (*c* 1.5, DMF); tlc R_f A 0.69, R_f B 0.69; amino acid analysis, Ala, 1.0, Pro, 1.0, Ser, 1.0, Gly, 1.1.

Anal. Calcd for $C_{27}H_{40}N_4O_8$ (548.6): C, 59.1; H, 7.3; N, 10.2. Found: C, 59.1; H, 7.4; N, 10.2.

N^{α},N^{ϵ}-Bis-*tert*-butyloxycarbonyl-L-lysyl-L-alanyl-L-prolyl-*O*-benzyl-L-serylglycine Ethyl Ester (VII).—The *tert*-butyloxycarbonyl group was removed from compound V (2.75 g, 5.0 mmol) as described above to give the trifluoroacetate VI (2.5 g, 90%): paper chromatography R_f A 0.62, R_f C 0.67; tlc R_f A 0.5, R_f C 0.5.

The tetrapeptide trifluoroacetate VI (2.5 g, 4.5 mmol) was suspended in CH_3CN (30 ml), and TEA (0.45 g, 4.5 mmol) and bis-*tert*-butyloxycarbonyl-L-lysine *p*-nitrophenyl ester[11] (2.55 g, 5.5 mmol) were added. The mixture was stirred overnight at room temperature. The excess of *p*-nitrophenyl ester was decomposed and the reaction mixture was worked up as described for the preparation of compound V. The sirupy crude product solidified on addition of ether to give 2.9 g (83%). For analysis, a sample was crystallized from MeOH–ether: mp 131–132°; $[\alpha]^{24}D$ −30° (*c* 1.67, DMF); tlc R_f A 0.70, R_f C 0.70; amino acid analysis, Lys, 1.0, Ala, 1.0, Pro, 1.2, Ser, 0.9, Gly, 0.9.

Anal. Calcd for $C_{38}H_{60}N_6O_{11}$ (776.9): C, 58.7; H, 7.8; N, 10.8. Found: C, 58.8; H, 7.90; N, 10.9.

N^{α},N^{ϵ}-Bis-*tert*-butyloxycarbonyl-L-lysyl-L-alanyl-L-prolyl-*O*-benzyl-L-serylglycine Hydrazide (VIII).—The protected pentapeptide ethyl ester VII (4.0 g, 5.15 mmol) was dissolved in MeOH (80 ml) and treated with hydrazine (1.8 g), and the solution was stored at room temperature for 4 days. The solvent was evaporated and the residue was dried *in vacuo* over concentrated H_2SO_4. The product was obtained from MeOH–ether as an amorphous solid (3.6 g, 80%): mp 100–105°; $[\alpha]^{24}D$ −66° (*c* 1.5, MeOH); tlc R_f A 0.63, R_f D 0.56.

Anal. Calcd for $C_{36}H_{58}N_8O_{10}$ (762.9): C, 56.7; H, 7.7; N, 14.7. Found: C, 56.8; H, 7.8; N, 14.5.

L-Lysyl-L-alanyl-L-prolyl-L-serylglycyl-L-arginine.—The protected pentapeptide hydrazide VIII (0.76 g, 1 mmol) was dissolved in DMF (6 ml) and the stirred solution was cooled to −20°. Concentrated HCl (0.5 ml, *ca.* 5.0 mmol) and then 2 *M* $NaNO_2$ solution (0.75 ml, 1.5 mmol) were slowly added. After 5 min at −15°, the temperature was lowered to −25°, and TEA (0.7 ml, 5 mmol) and nitro-L-arginine benzyl ester[12] (0.6 g, 2 mmol) were added. The mixture was kept at 4° for 3 days. The solvent was evaporated *in vacuo*, and the residue was partitioned between EtOAc and H_2O. The EtOAc layer was washed with cold 10% citric acid solution and 5% $NaHCO_3$, then dried over $MgSO_4$ and evaporated. The sirupy residue solidified under ether and the product, N^{α},N^{ϵ}-bis-*tert*-butyloxycarbonyl-L-lysyl-L-alanyl-L-prolyl-*O*-benzyl-L-serylglycylnitro-L-arginine benzyl ester, was filtered, washed with excess ether, and dried to give 0.9 g (85%): mp 94–95°; tlc R_f A 0.6; amino acid analysis, Orn + Lys, 1.45, Ala, 1.0, Pro, 1.0, Ser, 0.95, Gly, 1.0, Arg, 0.70 (nitroarginine content = 1.0 residue per mole, determined by uv absorption at 270 nm).

The protected hexapeptide (1.2 g, 1.14 mmol) was hydrogenated for 4 days in the presence of 10% Pd on charcoal catalyst (0.3 g) in a mixture of EtOH (20 ml) and AcOH (2 ml).

(19) M. Löw and L. Kisfaludy, *Acta Chim. Acad. Sci. Hung.*, **44**, 61 (1965).

The catalyst was removed and the solution was evaporated to dryness. The residue was dried *in vacuo* and washed with ether and EtOAc to give 0.9 g (88%) of N^{α},N^{ϵ}-bis-*tert*-butyloxycarbonyl-L-lysyl-L-alanyl-L-prolyl-L-serylglycyl-L-arginine: mp 191–193° (hygroscopic); $[\alpha]^{24}D$ −20° (*c* 1, DMF); tlc R_f A 0.35.

Anal. Calcd for $C_{53}H_{92}N_{10}O_{12}\cdot CH_3CO_2H\cdot 2H_2O$ (895.0): C, 48.8; H, 7.5; N, 15.4. Found: C, 48.3; H, 7.3; N, 15.8.

This partially blocked peptide (0.5 g, 0.56 mmol) was treated with TFA (10 ml) at room temperature for 30 min. The TFA was evaporated and the residue, after trituration under ether, was precipitated from MeOH with EtOAc to give 0.4 g: mp 170–175° dec; $[\alpha]^{24}D$ −21° (*c* 1, DMF); on paper R_f F 0.08, R_f C 0.05; does not move on tlc.

The hexapeptide ditrifluoroacetate (200 mg) was chromatographed on a column of Amberlite IRC-50 (2.5 × 30 cm) with ammonium acetate buffer, pH 6.5, of successively increasing ammonium ion concentration. Fractions of 7 ml each were collected and tested with Sakaguchi reagent. Tubes 240–275, eluted with 1.0 *M* buffer, contained X in electrophoretically homogeneous form. After lyophilization, 100 mg of pure peptide was obtained: amino acid analysis, Lys, 1.15, Arg, 0.95, Ser, 0.95, Pro, 1.0, Gly, 1.0, Ala, 1.0.

***N*-Benzyloxycarbonyl-L-valyl-L-serine Methyl Ester (XI).**—*N*-Benzyloxycarbonyl-L-valine (5.0 g, 20 mmol) and L-serine methyl ester hydrochloride (3.1 g, 20 mmol) were dissolved in CH_2Cl_2 (100 ml), and the solution was cooled to −4°. TEA (2.80 ml, 20 mmol) and DCC were added, in that order, and the mixture was stirred overnight. The precipitate was collected by filtration and washed with CH_2Cl_2 (100 ml). The combined filtrates were washed with 0.5 *M* HCl (3 × 70 ml), 1.0 *M* $NaHCO_3$ solution (3 × 70 ml), and H_2O (3 × 70 ml). On evaporation of the organic phase, a crystalline residue was obtained which was extracted with acetone (2 × 100 ml). The residue, mp 164–165°, was recrystallized from warm EtOH, mp 166–167°. The acetone washes were evaporated, and the crystalline residue was extracted several times with ether and then recrystallized from warm EtOH, mp 165–166°. A total of 3.5 g (50%) of product was thus obtained: $[\alpha]^{24}D$ −19° (*c* 1, methanol); tlc R_f B 0.90, R_f E 0.84.

Anal. Calcd for $C_{17}H_{24}N_2O_6$ (352.4): C, 57.9; H, 6.9; N, 8.0. Found: C, 58.2; H, 6.9; N, 8.1.

***N*-Benzyloxycarbonyl-L-nitroarginyl-L-valyl-L-serine Methyl Ester (XIII).**—The protected dipeptide XI (2.37 g, 6.75 mmol) was dissolved in a mixture of MeOH (120 ml) and 1 *M* HCl (7.3 ml), and the solution was hydrogenated for 4 hr in the presence of 10% Pd on charcoal catalyst (1.0 g). The solution was filtered, and the filtrate was evaporated to dryness at room temperature. The crystalline hygroscopic residue was dried overnight *in vacuo* to give XII, 1.7 g (100%), R_f B 0.55. It was dissolved in DMF (30 ml), and TEA (0.95 ml, 6.75 mmol) and *N*-benzyloxycarbonyl-L-nitroarginine pentachlorophenyl ester[15] (4.08 g, 6.75 mmol) were added, in that order, to the stirred solution. After 1 day, the solution was evaporated to dryness and the residue was triturated under an EtOAc (30 ml) and H_2O (20 ml) mixture. The white crystalline material (2.0 g, mp 184–186°) was filtered and washed with EtOAc and H_2O. A further crop of material (0.6 g) was obtained on concentration of the mother liquors. The two crops were combined and recrystallized from EtOH to give 2.24 g (60%): mp 185–187°; $[\alpha]^{24}D$ +3° (*c* 1, DMF); tlc R_f D 0.85, R_f B 0.9; amino acid analysis, Val, 1.0, Ser, 0.9, (NO_2) Arg (from uv absorption at 270 nm), 1.0.

Anal. Calcd for $C_{23}H_{35}N_7O_9$ (553.6): C, 49.9; H, 6.4; N, 17.7. Calcd for $C_{23}H_{35}N_7O_9\cdot H_2O$ (571.6): C, 48.3; H, 6.5; N, 17.2. Found: C, 47.9; H, 6.6; N, 17.1.

N^{α},N^{ϵ}-Bis-*tert*-butyloxycarbonyl-L-lysyl-L-alanyl-L-prolyl-L-serylglycine Hydrazide (XVI).—The protected pentapeptide ethyl ester VII (1.35 g, 1.74 mmol) was dissolved in a mixture of EtOH (50 ml) and AcOH (4 ml). The solution was hydrogenated for 2 days in the presence of a 10% Pd on charcoal catalyst (0.5 g). The catalyst was removed, the solution was evaporated, and the residue was dried *in vacuo*. On trituration under ether, an amorphous hygroscopic solid was obtained: 1.2 g (*ca.* 100%); mp 130° (sintering at 90°); $[\alpha]^{24}D$ −45° (*c* 1.2, DMF); tlc R_f A 0.65; the nmr spectrum showed the absence of aromatic protons.

The partially protected pentapeptide ester XV (2.29 g, 3.34 mmol) was dissolved in MeOH (50 ml) and treated with hydrazine (1 g). After 2 days, the solution was evaporated to dryness and the oily residue was dried over concentrated H_2SO_4 *in vacuo*. The glassy product was dissolved in EtOAc and precipitated by the addition of ether. The hygroscopic amorphous product (2.25 g, 98%) was collected: mp 130° (sintering at 90°); $[\alpha]^{24}D$ −38° (*c* 1.1, DMF); tlc R_f A 0.54, R_f C 0.66, R_f D 0.65.

N^{α},N^{ϵ}-Bis-*tert*-butyloxycarbonyl-L-lysyl-L-alanyl-L-prolyl-L-serylglycyl-L-arginyl-L-valyl-L-serine Methyl Ester Acetate (XVII). Azide Method.—Compound XIII (2.0 g, 3.62 mmol) was dissolved in MeOH (200 ml) and 1 *M* HCl (20 ml), and hydrogenated for 40 hr in the presence of 10% Pd on charcoal catalyst (1.0 g). The solution was filtered and evaporated to dryness, and the residue was lyophilized from H_2O. The glasslike product amounted to 1.6 g (100%); tlc R_f B, D 0.0; on paper chromatograms, R_f C 0.65. The product XIV was used as such in the preparation of octapeptide XVII.

The pentapeptide hydrazide XVI (2.7 g, 4 mmol) was dissolved in DMF (40 ml), and the stirred solution was cooled to −25°. A solution of 4.8 *M* HCl in dioxane (4 ml) was slowly added, followed by isoamyl nitrite (0.655 ml, 4.8 mmol). After 15 min at −25°, the solution was cooled to −50° and TEA (2.69 ml) was added, followed by a precooled solution of the tripeptide dihydrochloride XIV (1.6 g, 3.62 mmol) and TEA (0.51 ml, 3.62 mmol) in DMF (15 ml), and the funnel was rinsed with precooled DMF (3 ml). The solution was allowed to warm to −15°, and was stirred at this temperature for 1 hr. The reaction mixture was kept at 4° overnight and then concentrated *in vacuo*, and the residue was dried. The residue was dissolved in H_2O (20 ml) and freed from insoluble material by filtration. The filtrate and washings (30 ml) were applied to a column of Dowex 1X8 resin (40 × 2.5 cm, acetate cycle) and eluted with H_2O. The Sakaguchi positive part of the eluate (from 60–150 ml) was collected, lyophilized, and dried to give 3.7 g (89%) of crude product, tlc R_f B 0.51, R_f D 0.46 (an additional spot, R_f B 0.6, R_f D 0.6).

A sample (250 mg, from an earlier preparation) was dissolved in 0.05 *M* ammonium acetate (15 ml) and applied to a column of carboxymethylcellulose (Bio Rad Cellex-CM, 2.5 × 25 cm). The column was washed with 0.05 *M* ammonium acetate (50 ml) and fractions (150 drops, *ca.* 6 ml) were collected. It was then eluted, at a flow rate of 30 ml/hr, with a linear gradient from 0.05 *M* ammonium acetate (500 ml) to 0.5 *M* ammonium acetate (500 ml). Fractions 17–23 were combined and lyophilized to give 50 mg, tlc R_f B 0.6, R_f D 0.6. Fractions 26–36 were combined and lyophilized to give 190 mg (65%) of the purified product. For analysis, a sample was relyophilized several times from H_2O: mp 135–140° (sintering at 120°); $[\alpha]^{24}D$ −60° (*c* 1, methanol); tlc R_f B 0.51, R_f D 0.46; amino acid analysis, Lys, 1.1, Ala, 0.9, Pro, 1.1, Ser, 1.7, Gly, 0.9, Arg, 1.1, Val, 0.9.

Anal. Calcd for $C_{46}H_{82}N_{12}O_{17}$ (1075.2): C, 51.4; H, 7.69; N, 15.6. Calcd for $C_{46}H_{82}N_{12}O_{17}\cdot 4H_2O$: C, 48.2; H, 7.9; N, 14.7. Found: C, 48.0; H, 7.5; N, 15.0. Loss of weight on drying at 110°: calcd, 6.3%; found, 5.6%.

N^{α},N^{ϵ}-Bis-*tert*-butyloxycarbonyl-L-lysyl-L-alanyl-L-prolyl-L-serylglycyl-L-arginyl-L-valyl-L-serine Hydrazide Acetate (XVIII).—The octapeptide ester XVII (103 mg) was dissolved in MeOH (1.5 ml) and 97% hydrazine (100 mg) was added to the solution. After 24 hr, the solution was evaporated to dryness with a stream of N_2 and the residue was lyophilized twice from H_2O to give 98 mg: mp 121–126° (with gradual shrinking); $[\alpha]^{24}D$ −83° (*c* 0.5, H_2O); tlc R_f B 0.47, R_f D 0.30; amino acid analysis, Lys, 1.0, Ala, 1.0, Pro, 1.1, Ser, 2.0, Gly, 1.0, Arg, 1.0, Val, 0.9.

Anal. Calcd for $C_{43}H_{82}N_{14}O_{16}$: C, 50.3; H, 7.7; N, 18.2. Calcd for $C_{43}H_{82}N_{14}O_{16}\cdot 4H_2O$: C, 47.1; H, 7.9; N, 17.1. Found: C, 47.0; H, 7.5; N, 17.6. Loss of weight on drying at 110°: calcd, 6.3%; found, 5.4%.

***N*-*tert*-Butyloxycarbonyl-L-prolyl-*O*-benzyl-L-serylglycine Benzyl Ester (XXI).**—*O*-Benzyl-L-serylglycine benzyl ester hydrochloride (XX)[20] (3.7 g, 9.7 mmol) was dissolved in EtOAc (60 ml) and neutralized with TEA (1.36 ml, 9.7 mmol) at 0°. *tert*-Butyloxycarbonyl-L-proline (2.08 g, 9.7 mmol) and DCC (2.20 g, 10.7 mmol) were added successively, stirring was continued for 3 hr at 0°, and the reaction mixture was allowed to stand overnight. After the addition of AcOH (0.5 ml), the mixture was filtered and the filtrate was washed with 2% citric acid solution, brine, 5% $NaHCO_3$, and brine, successively. The EtOAc solution was dried over $MgSO_4$ and evaporated *in vacuo* to give a sirupy residue (5.5 g). The crude product (4.5 g) was dis-

(20) T. Hayakawa, K. Harada, and S. W. Fox, *Bull. Chem. Soc. Jap.*, **39**, 391 (1966).

tributed through 100 transfers in the solvent system $CHCl_3$–toluene–MeOH–H_2O (5:5:8:2). The purified tripeptide (3.35 g) was isolated from a band with $k = 0.20$, yield 78%. The distribution curve was identical with the one calculated for $k = 0.20$; $[\alpha]^{23}D$ −27° (*c* 2, EtOAc); tlc R_f B 0.74, R_f E 0.59.

Anal. Calcd for $C_{29}H_{37}N_3O_7$ (539.6): C, 64.6; H, 6.9; N, 7.8. Found: C, 64.6; H, 7.1; N, 7.8.

L-Prolyl-*O*-benzyl-L-serylglycine Benzyl Ester Trifluoroacetate (XXII).—The *tert*-butyloxycarbonyl group was removed from compound XXI (3.0 g) as described for compound IV to give the trifluoroacetate XXII (2.8 g, 91%; tlc R_f B 0.48). A sample was reprecipitated from EtOH–ether. Its melting point was unchanged.

Anal. Calcd for $C_{26}H_{30}N_3O_7F_3$ (553.6): C, 56.4; H, 5.5; N, 7.6; F, 10.3. Found: C, 56.3; H, 5.6; N, 7.6; F, 10.2.

N-*tert*-Butyloxycarbonyl-L-alanyl-L-prolyl-*O*-benzyl-L-serylglycine Benzyl Ester (XXIII).—*tert*-Butyloxycarbonyl-L-alanine *p*-nitrophenyl ester[10] (0.51 g, 1.65 mmol) was added to a suspension of XXII (1.0 g, 1.8 mmol) in $CHCl_3$ (25 ml) neutralized under ice cooling with TEA (0.25 ml, 1.64 mmol). The solution was stirred for 16 hr at room temperature and was kept slightly alkaline by the addition of TEA. After the evaporation of the solvent *in vacuo*, the residue was taken up in EtOAc, washed with 1 *M* NH_4OH, H_2O, 2% citric acid solution, and brine, and dried over $MgSO_4$. Evaporation gave a colorless, sirupy product which, on storage *in vacuo*, turned into an amorphous powder: 870 mg (87%); tlc R_f B 0.69, R_f E 0.49.

For further characterization, XXIII was converted into the corresponding hydrazide. A sample of XXIII (114 mg) and 97% hydrazine (100 mg) was dissolved in MeOH (2.0 ml) and allowed to react for 4 days at room temperature. After evaporation of the solvent, the residue was dried over P_2O_5 *in vacuo* and crystallized on trituration with ether. The residue was collected and washed with ether. Recrystallization from MeOH–ether gave 85 mg, mp 83–84°, $[\alpha]^{23}D$ −36° (*c* 1, MeOH).

Anal. Calcd for $C_{25}H_{38}N_6O_7$ (534.6): C, 56.2; H, 7.2; N, 15.7. Found: C, 55.8; H, 7.3; N, 15.6.

N^{α},N^{ϵ}-Bis-*tert*-butyloxycarbonyl-L-lysyl-L-alanyl-L-prolyl-L-serylglycine Pentachlorophenyl Ester (XXVII).—The protected tetrapeptide benzyl ester XXIII (2.0 g, 3.27 mmol) was dissolved in 95% TFA (3.0 ml) and allowed to react for 30 min. After evaporation of the TFA, addition of dry ether (50 ml) precipitated an oily product. The ether was removed by decantation and the residue was dried over NaOH pellets *in vacuo* to give an amorphous powder (2.04 g, 100%).

The trifluoroacetate XXIV (2.09 g, 3.34 mmol) was dissolved in EtOAc (35 ml) and neutralized under ice cooling with TEA (0.47 ml, 3.35 mmol). N^{α},N^{ϵ}-Bis-*tert*-butyloxycarbonyl-L-lysine *p*-nitrophenyl ester[11] (1.56 g, 3.33 mmol) was added, and the solution was stirred for 2 days at room temperature, while kept alkaline with the addition of a small amount of TEA. The product was taken up in EtOAc and treated as described for compound XXIII to yield an amorphous powder XXV (2.7 g, 96.4%): mp 59–66°; tlc R_f B 0.62, R_f E 0.54.

Compound XXV (2.1 g, 2.5 mmol) was dissolved in 95% EtOH (100 ml) and hydrogenated for 20 hr in the presence of a 10% Pd on charcoal catalyst (0.2 g). After removal of the catalyst, the solvent was evaporated *in vacuo*. The residue was dissolved in EtOAc (13 ml) and added to the complex[21] of pentachlorophenol (2.1 g, 7.9 mmol) and DCC (0.55 g, 2.7 mmol) in EtOAc (13 ml). The mixture was stirred at room temperature for 24 hr. After the addition of dry ether (30 ml), the residue was filtered and dissolved in dioxane (40 ml) and the DCU was removed by filtration. The filtrate was concentrated to dryness *in vacuo* and the residue was filtered with ether, yield 3.1 g. A sample (500 mg) was recrystallized from MeOH: 320 mg (82%); mp 167–173°; $[\alpha]^{23}D$ −35° (*c* 0.5, DMF); tlc R_f B 0.56, R_f E 0.65.

Anal. Calcd for $C_{35}H_{49}N_6O_{11}Cl_5 \cdot 3H_2O$ (961.1): C, 43.7; H, 5.8; N, 8.7; Cl, 18.4. Found: C, 43.7; H, 5.5; N, 8.8; Cl, 18.7. Loss of weight on drying at 110°: calcd, 5.6%; found, 5.1%.

Preparation of Compound XVII by the Active Ester Method.—L-Arginyl-L-valyl-L-serine methyl ester dihydrochloride (166 mg, 0.37 mmol), prepared as described earlier from protected tripeptide XIII, was suspended in DMF (3 ml) and neutralized with TEA (0.1 ml). The protected pentapeptide pentachlorophenyl ester (trihydrate) XXVII (363 mg, 0.37 mmol) was added to the solution and allowed to react for 40 hr, while the solution was kept alkaline with the addition of small amounts of TEA. The solvent was evaporated under a stream of N_2, and the residue was dissolved in $CHCl_3$ and extracted with H_2O. The aqueous layer was washed with $CHCl_3$ and EtOAc, and evaporated *in vacuo*. The residue was dissolved in H_2O, adsorbed in a column of Dowex 1X8 (acetate cycle, 40 × 2.5 cm), and eluted with distilled H_2O. The Sakaguchi positive fractions (60–140 ml) were pooled and lyophilized and the residue was dried *in vacuo*, yield *ca.* 250 mg. The residue was dissolved in a mixture of $CHCl_3$ and MeOH (1:1, 15 ml) and the filtered solution was applied to a column of silica gel (10 g, Baker 1.1 × 20 cm). The column was eluted first with the same solvent mixture (100 ml) and then with $CHCl_3$–MeOH (1:4, 100 ml). Compound XVII (50 mg) was recovered from the 1:1 mixture of the solvents, while the 1:4 mixture yielded some unchanged tripeptide ester XIV. The protected octapeptide ester was indistinguishable (tlc) from samples of XVII prepared by the azide method.

Registry No.—I, 34578-26-2; II, 34578-27-3; III, 34578-28-4; IV, 34578-29-5; V, 34578-30-8; VII, 34578-31-9; VIII, 34578-32-0; IX, 34578-44-4; X, 34578-33-1; XI, 34078-88-1; XIII, 34578-35-3; XVI, 34578-36-4; XVII, 34578-37-5; XVIII, 34578-38-6; XXI, 34578-39-7; XXII, 34578-40-0; XXIII hydrazide, 34578-41-1; XXV, 34578-42-2; XXVII, 34578-43-3; N^{α},N^{ϵ}-bis-*tert*-butyloxycarbonyl-L-lysyl-L-alanyl-L-prolyl-L-serylglycyl-L-arginine, 34578-45-5.

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(21) J. Kovacs, L. Kisfaludy, M. Q. Ceprini, and R. H. Johnson, *Tetrahedron*, **25**, 2555 (1969).

Rearrangement Reactions of 4-Bromoisophorone[1]

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4-Bromoisophorone (Ib) is shown to undergo two types of rearrangment reactions with nucleophiles: eliminative aromatization to 3,4,5-trimethylphenol (XI) and 2,3,5-trimethylphenol (XII), and SN2′ attack, followed by double bond migration, to give 2-substituted isophorone derivatives III. The report of direct SN2 substitution to yield 4-substituted isophorone derivatives is shown to be in error. Thus, reaction of Ib with NaOH gives the two phenols XI and XII, as well as 2-hydroxyisophorone (IIIc) and the six dimers IV–IX, derived from O- and C-alkylation of the phenols XI and XII by 4-bromoisophorone. The reaction with silver acetate gives the phenols XI and XII, the dimer X, derived from oxidative coupling of XI, and the allylic acetate IId. Reaction with sodium iodide gives the allylic iodide IIe, which gives mainly XI but no XII when treated with NaOH or AgOAc.

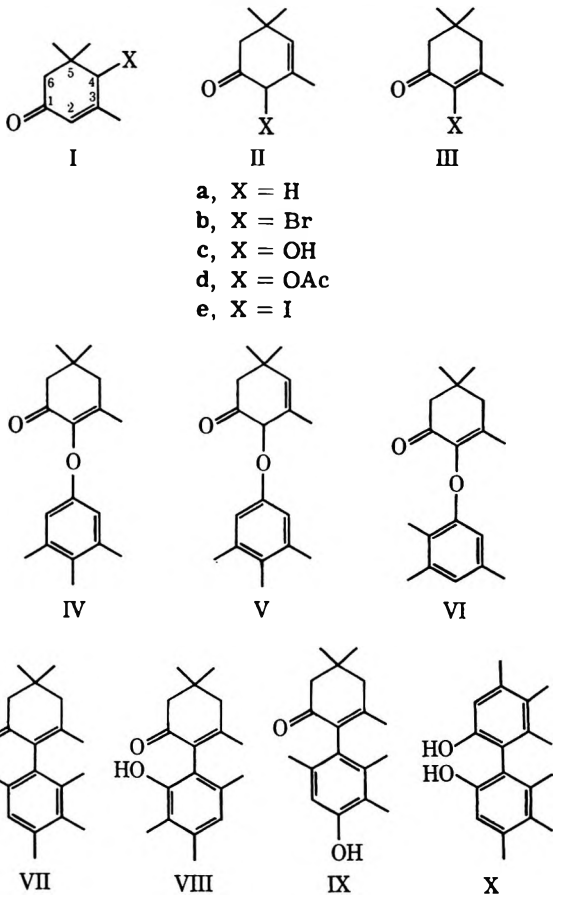
In 1957, Edgar, Harper, and Kazi[3] reported the synthesis of 4-bromoisophorone (Ib) and some substitution reactions it undergoes, including its hydrolysis in base to 4-hydroxyisophorone (Ic). In connection with terpene syntheses, we desired a less temperamental route to 4-hydroxyisophorone than that afforded by the usual route through deconjugation of isophorone (Ia) to β-phorone (IIa).[4,5] We have therefore tried to repeat the work of Edgar, Harper, and Kazi and find that in our hands only rearrangement products are formed from 4-bromoisophorone in base-catalyzed hydrolysis or reaction with silver acetate.

Most allylic oxidants react with isophorone at the C-6 and/or the C-7 positions,[6] rather than at C-4, presumably for steric reasons. However, the reaction of isophorone with *N*-bromosuccinimide gives 4-bromoisophorone in about 50% yield, as reported.[3] The nmr, uv, and ir spectra are in accord with this formulation. Although the nmr spectrum for 6-bromoisophorone would also be expected to be very similar to that observed, the allylic coupling (J = 1 Hz) observed between the C-2 and C-4 proton signals verifies that the compound actually is 4-bromoisophorone.[7]

The reaction of 4-bromoisophorone with aqueous $NaHCO_3$ is reported[3] to lead to a compound assumed to be 4-hydroxyisophorone (Ic) (not obtained pure)[9] and 3,4,5-trimethylphenol, in about equal amounts, as the only distillable materials. In our hands, a number of products were obtained, including 3,4,5-trimethylphenol and much starting material, but no 4-hydroxyisophorone (Ic) could be detected. In particular, the nmr spectrum of the total reaction mixture showed no peaks in the τ 4–6 region except those of the starting material, thus revealing the absence of the C-2 and C-4 protons of 4-hydroxyisophorone.[4c]

More vigorous reaction conditions or the use of NaOH instead of $NaHCO_3$ gave rise to complete reaction of the 4-bromoisophorone. Under the latter conditions, nine products were isolated and identified. The base-soluble compounds were identified as 3,4,5-trimethylphenol (12%), 2,3,5-trimethylphenol (4%), and the diosphenol, 2-hydroxyisophorone (IIIc) (5%), by comparison with authentic samples. The neutral fraction of the reaction mixture contained six new dimeric compounds, which were separated by column chromatography and crystallization. They are all products derived from attack of the anions of the two initially formed phenols on 4-bromoisophorone, and are assigned structures IV through IX (Chart I) on the basis of their

CHART I



(1) Reported at Southeast–Southwest Regional Meeting of the American Chemical Society, New Orleans, La., Dec 3, 1970, Abstract #440.

(2) Robert A. Welch Undergraduate Research Scholars.

(3) A. J. B. Edgar, S. H. Harper, and M. A. Kazi, *J. Chem. Soc.*, 1083 (1957).

(4) (a) M. S. Kharasch and P. O. Tawney, *J. Amer. Chem. Soc.*, **63**, 2308 (1941); (b) O. Isler, H. Lindlar, M. Montavon, R. Ruegg, G. Saucy, and P. Zeller, *Helv. Chim. Acta*, **39**, 2041 (1956); (c) J. N. Marx and F. Sondheimer, *Tetrahedron, Suppl. VIII*, Part I, 1 (1966).

(5) Since this work was carried out, an improved procedure for the synthesis of β-phorone has been reported: J. Meinwald and L. Hendry, *J. Org. Chem.*, **36**, 1446 (1971).

(6) (a) J. W. Ellis, *ibid.*, **34**, 1154 (1969); (b) E. M. Kosower and G.-S. Wu, *ibid.*, **28**, 633 (1963); (c) W. von E. Doering and F. J. Beringer, *J. Amer. Chem. Soc.*, **71**, 2221 (1949).

(7) The reaction of isophorone with bromine in CCl_4, on the other hand, gives a very complex mixture of bromination products, and the HBr salt of isophorone crystallizes from the mixture.[8] However, the use of solid $NaHCO_3$ in large excess to remove the HBr as it is formed gives rise to 4-bromoisophorone (Ib) as the major product. The yield is almost quantitative on a small scale, at −10°, but decreases dramatically on scaling up the reaction, so that the use of NBS is the preferred route.

(8) J. N. Marx, *Tetrahedron Lett.*, **No. 40**, 3517 (1970).

(9) The uv and ir spectra reported for the impure compound assumed to be 4-hydroxyisophorone (Ic) could also be accommodated by the diosphenol IIIc.

nmr spectra (see Experimental Section) and their independent syntheses.

The major neutral product (50%) was identified as the dimeric ether IV. Its nmr spectrum showed two equivalent methyl groups and two equivalent protons attached to an aromatic ring as well as one other aromatic methyl group and protons characteristic of a 2-substituted isophorone derivative. Compound IV was synthesized independently in high yield from the reaction of sodium 3,4,5-trimethylphenoxide with 4-bromoisophorone, thus completing its structure proof. The only other product formed in this reaction was a phenolic ketone, whose spectral data and method of synthesis identified it as VII. Compound VII was also identified as a minor product from the original reaction of 4-bromoisophorone with NaOH.

Some chromatographic fractions containing the dimeric ether IV were contaminated with a very similar compound, which showed all the same nmr peaks, but the singlet in the aromatic region at τ 3.49 integrated for about three protons instead of two. This signal could be resolved into two signals at τ 3.45 and 3.57 by use of benzene as the nmr solvent. Pure IV showed only the τ 3.45 peak under these conditions. The uv spectrum showed the 242-nm peak due to IV, as well as end absorption and weak absorption at 280 (aromatic ring) and 300 nm (carbonyl). The contaminant was assigned the nonconjugated structure V, which is the assumed precursor of IV. Attempts at further purification of the mixture failed, but treatment with NaOH converted it completely into the conjugated compound IV, thus verifying the structural assignment. Several attempts to synthesize pure V from sodium 3,4,5-trimethylphenoxide and 4-bromoisophorone under mild conditions gave only IV.

Another dimer isolated from the original reaction mixture was the ether VI derived from attack of 2,3,5-trimethylphenoxide on 4-bromoisophorone. Its nmr spectrum showed three nonequivalent methyls and two nonequivalent hydrogens on the aromatic ring. It could be synthesized in high yield from the reaction of sodium 2,3,5-trimethylphenoxide with 4-bromoisophorone. This reaction also gave two minor phenolic ketone dimers, identified as VIII and IX, which were also isolated from the original reaction mixture. Although the nmr spectra did not allow unambiguous structural assignments, VIII is identified as the ortho-substituted phenol, since it formed a stable crystalline chelate with $FeCl_3$ (as did VII) but the para isomer IX gave only a green color.

Thus, 4-bromoisophorone (Ib) undergoes two fundamental types of reactions in aqueous base, aromatization and substitution with allylic rearrangement (S_N2'). The compound can be considered as a neopentyl allylic bromide, for which direct elimination reactions are impossible. The present work demonstrates that direct S_N2 reactions do not occur, presumably because the 4 position is very sterically blocked. However, the 2 position is more sterically accessible, and nucleophilic attack there occurs readily. Attack of hydroxide ion leads to the diosphenol IIIc, but aromatization competes. As the anions derived from XI and XII build up, they attack the 4-bromoisophorone in the S_N2' manner, both through oxygen and carbon, giving rise to the dimers IV–IX. This reaction is very efficient, in accord with the greater nucleophilicity expected for phenoxides over hydroxide, as shown by the fact that no aromatization occurred when the preformed phenoxides were allowed to react with 4-bromoisophorone.[10] In these reactions, the deconjugated isomers doubtlessly are formed first and are isomerized by the base to the more stable conjugated isomers, but except for V they could not be detected.

Edgar, Harper, and Kazi[3] report that the reaction of AgOAc with 4-bromoisophorone occurs without rearrangement to give 4-acetoxyisophorone (Id). However, we can detect no product which has the expected nmr spectrum. Four products have been isolated from this reaction, in yields quite dependent on the exact reaction conditions. These are 3,4,5-trimethylphenol (XI) (30–80%), 2,3,5-trimethylphenol (XII) (5–15%), the allylic acetate IId (5–10%), and the phenolic dimer X (5–15%). In addition, a complex mixture of unidentified compounds was formed if the reaction was not protected from the air.

The uv and ir spectra of the allylic acetate IId were characteristic of a nonconjugated cyclohexenone. Its nmr spectrum showed one vinyl proton signal at τ 4.18 and one proton signal at τ 4.54. This latter is consistent with the C-2 proton in IId, deshielded by three electronegative groups. For comparison, the C-4 proton signal of Ib appears at τ 5.67.

The phenolic dimer X could be synthesized independently by oxidative coupling of 3,4,5-trimethylphenol with AgOAc, and doubtlessly arises from this source in the original reaction. This suggestion is strengthened by the fact that metallic silver is also formed in the reaction.

Thus, the reaction with AgOAc gives mainly aromatization, but the allylic acetate IId is formed as a product of S_N2' attack. Under the more neutral conditions of the AgOAc reaction, the double bond does not migrate into conjugation, as in the NaOH reaction above. However, the double bond probably does migrate thermally, since IId has an identical retention time with that of authentic IIId, prepared by acetylation[11] of diosphenol IIIc, on three different gas chromatographic columns.[12]

The aromatization reaction requires comment, especially to explain the formation of 2,3,5-trimethylphenol (XII). The reaction must involve carbonium ion formation, followed by a 1,2 shift of a methyl group,[13] and proton loss (Chart II), since the ratio of 3,4,5-trimethylphenol and its further transformation products to 2,3,5-trimethylphenol and its products is *ca.* 10:1 from either the reaction of NaOH or AgOAc on 4-bromoisophorone (Ia). The allylic carbonium ion A formed initially, however, should be destabilized

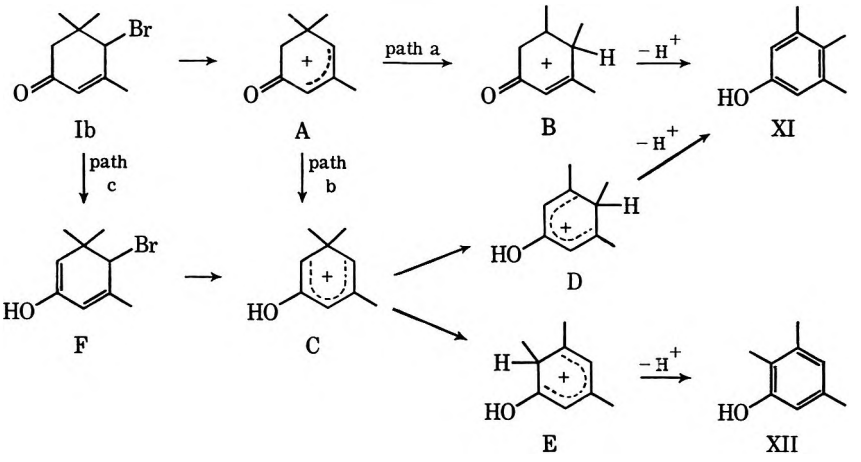
(10) Besides the reactions mentioned in the structure proof, the reaction of 4-bromoisophorone with *p*-cresol in base gave only the ether and phenolic ketone analogous to IV and VI derived from the *p*-cresol.

(11) C. Maignan, J. C. Grandguillot, and F. Rouessac, *Bull. Soc. Chim. Fr.*, 2019 (1970).

(12) The "4-acetoxyisophorone" obtained by Edgar, Harper, and Kazi[3] by distillation of the reaction mixture is probably IIId, although we did not obtain enough of the product to distil it and prove the point, since a large-scale run gave almost only phenolic material. Doubtlessly, the chrysamanthate esters these authors report have rearranged structures also, but this was not investigated.

(13) A referee has suggested that the formation of 2,3,5-trimethylphenol could also be rationalized by a 1,4-methyl migration in ion A. This is ruled out by the fact that the iodo compound IIe gives no 2,3,5-trimethylphenol, yet must rearrange through the ion A.

CHART II



by the adjacent carbonyl group.[14] To avoid this difficulty, the methyl migration could be rather concerted with ionization of the bromide (path a), such that a large amount of positive charge density will not accumulate during the rearrangement step. Alternatively, the ion A can enolize to give the ion C, in which migration can occur to either side, or else ion C could be derived from the enol F (path c). The ion C would be expected to have greater positive charge density at the 4 position than at the 6 position (equivalent to the 2 position in the phenols), and so the *ca.* 10:1 ratio of the phenols XI and XII might be explained without invoking ion A. The enol F would be expected to ionize readily, and thus we favor path c instead of a competition between paths a and b to explain the results. In the NaOH reaction, the zwitterion derived from ion C by proton abstraction may be the actual intermediate, but the arguments are similar.

With the failure to obtain products of direct substitution of 4-bromoisophorone, we attempted to synthesize 4-iodoisophorone (Ie), in order to investigate the effect of a better leaving group on the substitution reactions. However, treatment of Ib with excess NaI in DMSO gave only the allylically rearranged iodide IIe. This compound decomposes slowly on storage, and reacts very rapidly with nucleophiles. For example, the reaction with NaOH gives almost exclusively 3,4,5-trimethylphenol (XI) and diosphenol (IIIc). Interestingly, no 2,3,5-trimethylphenol could be detected. This suggests that the enolic carbonium ion C (Chart II) is not formed in this case, probably because the iodide is a better leaving group and is in a more sterically open environment; so the postulated concerted methyl migration in ion A would be much more favored in this case.[13]

Treatment of the iodo compound IIe with AgOAc gave almost only 3,4,5-trimethylphenol but no 2,3,5-trimethylphenol. The minor products were the allylic acetate IId, an unidentified compound detectable by vpc, and some isophorone (Ia). The latter probably arose from some decomposition of the starting material, since free iodine is slowly liberated during its formation and handling.

Experimental Section

Bromination of Isophorone (Ia).—To a rapidly stirred mixture of 0.20 g (1.45 mmol) of isophorone in 10 ml of CCl_4 and 1 g of solid $NaHCO_3$ in an ice–salt bath was added 0.23 g (1.45 mmol) of bromine in 5 ml of CCl_4 dropwise over the period of 1 hr. After another 2 hr decolorization was complete. The solid was removed by filtration. The nmr spectrum ($CDCl_3$) showed only the characteristic peaks of 4-bromoisophorone: τ 8.84, 8.73 (3 H each, s, C-5 Me's), 7.87 (3 H, d, J = 1 Hz, C-3 Me), 7.88, 7.37 (1 H each, AB quartet, J = 16 Hz, C-6 H's), 5.67 (1 H, d, J = 1 Hz, C-4 H), 4.13 (1 H, p, J = 1 Hz, C-2 H). Removal of the CCl_4 below 40°, the last traces at 0.1 mm, and crystallization from minimum ether gave 0.27 g in two crops of 4-bromoisophorone (85%), mp 55–57° (lit.[3] mp 48–49°), identical with a sample prepared according to ref 3.

In a 20-g scale run (6 hr required for decolorization of Br_2), the nmr spectrum showed a complex mixture of products. By integration of the τ 5.67 peak, it was estimated that 35–40% of the material was 4-bromoisophorone.

Reaction of 4-Bromoisophorone with NaOH.—To a stirred solution of 7.34 g (184 mmol) of NaOH in 150 ml of H_2O was added 20.0 g (92.4 mmol) of 4-bromoisophorone. The mixture was stirred for 48 hr at 25° and was almost neutral, then was separated into a base-soluble fraction (2.8 g) and an ether-soluble fraction (10.3 g).

The base-soluble fraction contained three compounds, as detected by vpc (6 ft × 0.125 in. Apiezon L on Chromosorb G at 200°), identified in order of increasing retention times as the diosphenol IIIc (25%), 2,3,5-trimethylphenol (18%), and 3,4,5-trimethylphenol (57%). The compounds were separated by column chromatography over silica gel (standard chromatographic conditions, a 25 × 1.5 cm column of silica gel was packed in 5% ether–95% petroleum ether (bp 30–60°) by volume; the column was eluted with increasing amounts of ether, given as percentages). Elution with 20% ether gave a mixture of diosphenol III, contaminated with some 2,3,5-trimethylphenol. Sublimation at 0.1 mm gave a pure sample of the diosphenol III, mp 91–93°, identical with an authentic sample, prepared by permanganate oxidation of isophorone[15] or HCl rearrangement of isophorone oxide.[16] Fractions from the column eluted with 25% ether were rich in 2,3,5-trimethylphenol. Crystallization from water gave a pure sample, mp and mmp 93–95°. Fractions eluted with 40% ether gave almost pure 3,4,5-trimethylphenol, crystallized from water, mp and mmp 106–107°.

Direct crystallization from ethanol of the neutral fraction of the original reaction mixture gave 3.5 g (three crops, after recrystallization) of IV: mp 110–111°; uv λ_{max}^{EtOH} 228, 243, 281 nm (shoulder); ir ν_{KBr} 1695, 1640, 1620, 1575 cm^{-1}; nmr ($CDCl_3$) singlets at τ 8.88 (6 H, C-5 Me's), 8.13 (3 H, C-3 Me), 7.94 (3 H, C-4′ Me), 7.79 (6 H, C-3′ and C-5′ Me's), 7.60 (4 H, C-4 and C-6 H's), 3.49 (2 H, aromatic H's).

(14) L. Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1948, p 199.

(15) O. Wallach, *Justus Liebigs Ann. Chem.*, **414**, 329 (1916).

(16) G. B. Payne, *J. Org. Chem.*, **24**, 719 (1959).

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.25; H, 8.99.

The mother liquor material was chromatographed on silica gel, using the standard technique described above, using a 3 × 75 cm column. Fractions (50 ml) were collected and recombined on the basis of tlc and nmr analysis. Fractions 1–4 (5% ether in petroleum ether) were empty. Fractions 5–7 (10%) (0.2 g) gave no characterizable material. Fractions 8–9 (10%) (0.1 g) were rechromatographed on silica gel. Crystals of VI (35 mg) were obtained in the 10% fractions: mp 138–140° (EtOH); uv λ_{max}^{EtOH} 228, 243, 281 nm; ir ν_{CCl_4} 1695, 1645, 1620, 1580 cm^{-1}; nmr (CCl_4) all singlets at τ 8.85 (6 H, C-5 Me's), 8.13 (3 H, C-3 Me), 7.82, 7.82, 7.77 (3 H each, aromatic Me's), 7.72 and 7.63 (2 H each, C-4 and C-6 H's), 4.02 and 3.48 (1 H each, aromatic H's).

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.13; H, 8.79.

Chromatography fractions 10–16 (15 and 20%) (2.3 g) gave 0.72 g of IV, mp 110–111°, by crystallization from ethanol. Rechromatography of the mother liquor material on silica gel gave further amounts of IV. The 15% fractions, however, contained mixtures of IV and a very similar compound. Very careful rechromatography of these combined fractions gave, in the 10% fractions after extensive elution, material of mp 95–115°, which was a *ca.* 1:1 mixture of IV and the nonconjugated isomer V. The nmr spectrum of the mixture was almost superimposable on that of compound IV. However, the τ 3.49 signal integrated for about three protons instead of two. Addition of 10% benzene resolved this signal into two peaks at τ 3.45 (due to IV) and 3.57. The uv spectrum shows stronger end absorption, enhanced absorption at λ_{max} 280, and a new low-intensity absorption at 300 nm. Treatment of a portion of the mixture with 5% NaOH for 2 hr at 25° with stirring, followed by acidification and ether extraction, gave only IV, mp 110–111°. Lack of material precluded further characterization or purification of V.

Fractions 17–27 from the original chromatogram (20–35%) (0.3 g) were rechromatographed on silica gel. Only IV, followed by 3,4,5-trimethylphenol and 2,3,5-trimethylphenol, were detected.

Fractions 28–29 (40%) (0.5 g) were rechromatographed on silica gel. The 20% fractions contained VIII (150 mg), difficultly crystallizable from petroleum ether: mp 156–157°; uv λ_{max}^{EtOH} 221, 245, 288 nm; ir ν_{KBr} 3380, 1650, 1620, 1600, 1570 cm^{-1}; nmr ($CDCl_3$), s at τ 8.87 (6 H, C-5 Me's), 8.27 (3 H, C-3 Me), 8.02, 7.89, 7.77 (3 H each, aromatic Me's), 7.58 (4 H, C-4 and C-6 H's), 3.30 (1 H, aromatic H).

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.46; H, 8.64.

To a chloroform solution of VIII was added $FeCl_3$ in chloroform. Addition of a few drops of pyridine gave an orange-brown iron chelate containing pyridine: mp 107–110°; ir ν_{KBr} 2375, 1610, 1530, 745, and 675 cm^{-1}. No signals were detectable by nmr.

Original chromatogram fractions 30–39 (40–65%) (2.1 g) were rechromatographed on silica gel. Fractions eluted with 20–30% gave 40 mg of VII, difficultly crystallizable from petroleum ether: mp 161–165°; uv λ_{max}^{EtOH} 221, 245, 288 nm; ir ν_{KBr} 3330, 1660, 1630, and 1580 cm^{-1}; nmr ($CDCl_3$), all singlets at τ 8.84 (6 H, C-5 Me's), 8.38 (3 H, C-3 Me), 8.09, 8.09, 7.95 (3 H each, aromatic Me's), 7.56 (4 H, C-4 and C-6 H's), 3.70 (1 H, aromatic H).

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 78.94; H, 8.80.

The compound formed an orange-brown ferric chelate in the presence of pyridine, mp 155–157°. Not enough material was available for further characterization.

Further elution of the column from the rechromatography of original fractions 30–39 gave, in the 30–40% fractions, 25 mg of compound IX, difficultly crystallizable from petroleum ether: mp 142–145°; uv λ_{max}^{EtOH} 222, 244, 291 nm; ir ν_{KBr} 3330, 1650, 1635 (sh), 1620 (sh), 1560 cm^{-1}; nmr ($CDCl_3$) all singlets at τ 8.87 (6 H, C-5 Me's), 8.29 (3 H, C-3 Me), 8.04, 7.91, 7.79 (3 H each, aromatic Me's), 7.58 (4 H, C-4 and C-6 H's), 3.41 (1 H, aromatic H).

This compound gave a green color with $FeCl_3$ and pyridine in $CHCl_3$, but no chelate could be obtained.

Reaction of 4-Bromoisophorone with Silver Acetate.—A stirred mixture of 20.01 g of 4-bromoisophorone and 15.75 g of silver acetate in 150 ml of glacial acetic acid was heated at 90° for 3 hr as reported.[3] A finely divided precipitate of metallic silver and AgBr formed. The mixture was filtered, diluted with water, extracted with ether, washed with $NaHCO_3$ and then water, and dried over $MgSO_4$, and the solvent was removed to give 19.51 g of material showing much starting material (strong Beilstein test) and several new peaks by nmr analysis. The material was dissolved in 150 ml of acetic acid, another 10.00 g of AgOAc was added, and the mixture was heated at 80° for 17 hr. After work-up as before, 11.20 g of material was obtained. The viscous oil deposited, in three crops, 0.40 g of the phenol dimer X: mp 240–241° (acetone); uv λ_{max}^{EtOH} 286 nm (ϵ 10,600); $\lambda_{max}^{EtOH+NaOH}$ 304 nm; ir ν_{max}^{KBr} 3500, 1610, 1570, 860 cm^{-1}; nmr ($CDCl_3$) τ 8.07, 7.78, 7.71 (3 H each, s), 3.27 (1 H, s).

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.82; H, 8.13.

A solution of X in concentrated H_2SO_4 showed nmr peaks at *ca.* τ 7.3, 7.7, and 8.0 (3 H each, s). This is consistent with sulfonation of X ortho to the phenol. No attempt was made to isolate the sulfonated product.

On treatment of X with acetic anhydride in pyridine overnight at room temperature, the corresponding diacetate was obtained: mp 132.9–133.5° (from ether); nmr ($CDCl_3$) τ 8.13 (3 H, s, OAc), 8.08, 7.80, 7.67 (3 H each, s, Me's), 3.18 (1 H, s).

To a solution of 1.006 g of 3,4,5-trimethylphenol was added 1.229 g of AgOAc in 10 ml of HOAc. The mixture was stirred and heated at 80° for 15 hr. Silver metal was filtered off, and the products were recovered by ether extraction. Crystallization from 5 ml of ether gave 0.102 g (10.2%) of X, mp 238–240°. The material remaining in the mother liquors was almost pure 3,4,5-trimethylphenol, as judged by the nmr spectrum.

The material remaining in the mother liquors from the original reaction of 4-bromoisophorone with AgOAc, after removal of X, was extracted well with 10% NaOH. The material recovered after acidification of the base layer was identified by vpc and nmr analysis as a 80:20 mixture of 3,4,5-trimethylphenol (XI) and 2,3,5-trimethylphenol.

The neutral material from the above extraction (5.8 g) was absorbed on 50 g of silica gel and placed on top of a column of 350 g of silica gel packed with 10% ether–90% petroleum ether (bp 40–60°). Fractions of 50 ml were collected, and the progress of the chromatogram was monitored by nmr analysis. Most fractions contained complex mixtures of products which could not be identified or purified further. However, fractions eluted with 25% ether–75% petroleum ether gave 0.696 g of material which was mainly the allylic acetate IId. Rechromatography gave a pure sample: uv, end absorption; ir $\nu_{max}^{CCl_4}$ 1710, 1725, 1670 cm^{-1}; nmr τ 9.02 and 8.99 (3 H each, s, C-5 Me's), 8.14 (3 H, d, J = 1 Hz, C-3 Me), 7.89 (3 H, s, OAc), 7.75 (2 H, s, C-6 H's), 4.54 (1 H, d, J = 1 Hz, C-2 H), 4.18 (1 H, p, J = 1 Hz, C-4 H). This compound had an identical retention time with that of a sample of IIId,[9] prepared by treatment of the diosphenol IIIc[8] with Ac_2O (reflux overnight, followed by evaporation of the Ac_2O; this compound hydrolyzes rather easily) on SE-30, DEGS, and Apiezon L vpc columns at 120–200°, suggesting that isomerization was occurring at these temperatures.

In another run, 20.00 g of AgOAc and 20.00 g of 4-bromoisophorone were refluxed for 17 hr in 150 ml of glacial acetic acid under N_2 with protection from light. Silver metal was still formed, but the total reaction mixture was much less complex. Direct crystallization from the recovered oily product mixture gave 1.42 g (12.2%) of the dimer X. Nmr analysis of the remaining material showed mostly 3,4,5-trimethylphenol, which could be obtained by direct crystallization from ethanol. Gas chromatography showed only 3,4,5-trimethylphenol (76%), 2,3,5-trimethylphenol (19%), and the allylic acetate (5%).

Reaction of 4-Bromoisophorone with NaI. Allylic Iodide IIe.[17]—To a solution of 5.00 g (23.5 mmol) of 4-bromoisophorone (Ib) in 50 ml of dimethyl sulfoxide was added 5.00 g (34.75 mmol) of NaI at room temperature with protection from light. After 10 min of stirring, solution was complete. After 24 hr, water was added, the mixture was extracted well with ether, washed with $NaHSO_3$ to remove I_2, washed with water, and dried over $MgSO_4$, and the ether was removed at the aspirator below 20° to give 5.25 g of product. Nmr analysis showed that the product was *ca.* 65% of unreacted 4-bromoisophorone (Ib) and 35% of the allylic iodide IIe, by the ratio of the peaks at τ 5.67 and 5.53, respectively. The material was resubmitted for a further 24 hr with 5.00 g of NaI in 50 ml of DMSO. Nmr

(17) We thank Don Guion for developing this reaction.

analysis now revealed that the reaction was 80% complete. After the product was resubmitted to the reaction conditions for a further 24 hr, the starting material Ib was not detectable by nmr. The product (3.02 g), which was very unstable and liberated iodine on standing or heating, had an nmr spectrum as follows: τ 8.77, 8.69 (3 H each, C-5 Me's), 7.77 (3 H, d, J = 1 Hz, C-3 Me), 7.75 (2 H, broad s, C-6 H's), 5.53 (1 H, d, J = 1 Hz, C-2 H), 4.13 (1 H, p, J = 1 Hz, C-4 H). Peaks for small amounts of contaminants could be observed in the upfield region in all preparations of IIe, but the compound could not be purified, so it was used immediately in subsequent reactions. In one run the reaction was allowed to proceed for 2 weeks, but a 40:60 ratio of IIe to Ib remained.

An 0.0413-g sample of IIe, when treated with excess $AgNO_3$, gave 0.0219 g of AgI (calcd 0.0224 g).

Reaction of Iodide IIe with NaOH.—To a stirred solution of 0.32 g of NaOH in 10 ml of H_2O was added 1.0 g of freshly prepared IIe. After 15 min at room temperature, the reaction mixture had become almost neutral. Analysis of the product by vpc and nmr revealed 70% 3,4,5-trimethylphenol (XI) and 25% diosphenol IIIc and small amounts of isophorone and unidentified substances. 2,3,5-Trimethylphenol (XII) was shown to be absent.

Reaction of Iodide IIe with AgOAc.—To a stirred solution of 2.51 g of AgOAc in 20 ml of glacial HOAc was added 2.0 g of freshly prepared IIe. The reaction mixture, protected from light and air, was stirred for 15 min at room temperature, then heated to 80° for 20 min. Filtration and ether extraction gave 0.80 g of material which was separated into base-soluble (0.40 g) and neutral (0.37 g) fractions. Gas chromatographic analysis revealed that the neutral layer contained 45% of the allylic acetate IId, 15% of isophorone, and 40% of an unidentified product. The base-soluble material was 3,4,5-trimethylphenol (70%) and diosphenol IIc (30%).

Registry No.—Ib, 16004-91-4; IId, 34638-12-5; IIe, 34638-13-6; IIIc, 34638-14-7; IV, 34638-15-8; V, 34638-16-9; VI, 34638-17-0; VII, 34638-18-1; VIII, 34638-19-2; IX, 34638-20-5; X, 34638-21-6; X diacetate, 34638-22-7.

Acknowledgment.—We wish to thank the Robert A. Welch Foundation for support of this work.

The Chemistry of the *trans*-Trimethylenenorbornene Ring System. I. A General Synthesis of 9,9-Disubstituted *trans*-5,6-Trimethylene-2-norbornene Derivatives[1a,b]

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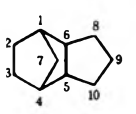
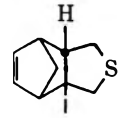
Condensation of *trans*-5,6-dimethylol-2-norbornene ditosylate and diethyl malonate with potassium *tert*-butoxide in *tert*-butyl alcohol afforded a mixture of cyclized products from which 9,9-dicarbo-*tert*-butoxy-*trans*-5,6-trimethylene-2-norbornene was readily separable. Saponification of the remaining ester mixture then gave the corresponding dicarboxylic acid. Attempts to prepare related *trans*-trimethylenenorbornenes by Dieckmann cyclization of *trans*-5,6-dicarbethoxymethyl-2-norbornene or the corresponding dimethyl ester and by Thorpe–Ziegler cyclization of *trans*-5,6-dicyanomethyl-2-norbornene were unsuccessful. Infrared and nmr spectra of the cyclized products were interpreted in terms of a high degree of internal strain associated with the *trans*-trimethylene bridge. It was concluded that unusually large distortions of the norbornyl cage occur in these compounds and that the norbornyl cage shows an unexpectedly high capability of accommodating strain.

The dicyclopentadienes[2,3] are known to exist in two distinct isomeric modifications (**1a** and **1b**) having either the endo,cis or exo,cis ring junction.[4] The possibility that similar derivatives containing a trans ring junction might also be prepared was first considered in 1932 but was rejected at that time on steric grounds.[4] A trans structure was later proposed[5] for a product obtained from the isomerization of tetrahydro-*endo*-dicyclopentadiene, but this was subsequently shown to be incorrect.[6] In 1965, however, Wilder and Feliu-Otero reported[7] the sulfide **2**, an heterocyclic derivative of dicyclopentadiene which incorporates a trans five-membered ring. Bachman[8] had previously suggested the *trans*-trimethylenenorbornane **3** as one of several products obtained from the decomposition of certain



1a, endo, cis
b, exo, cis



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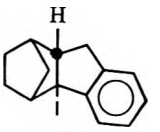

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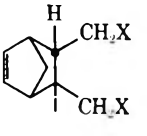


4, X = OTs
5, X = CN
6, X = COOH
7, X = $COOCH_3$
8, X = $COOC_2H_5$

(1) (a) Grateful acknowledgment is made to the Petroleum Research Fund administered by the American Chemical Society for partial support of this work. (b) Presented in part at the 3rd Central Regional Meeting of the American Chemical Society, Cincinnati, Ohio, June 1971. (c) Taken in part from the M.A. Theses of M. N. E. and R. L. T., Bowling Green State University, Bowling Green, Ohio, 1970–1971.

(2) Of the several systems of nomenclature that have been applied to compounds in this series, the semitrivial *trans*-trimethylenenorbornene system based on that proposed by Schleyer and Donaldson[3] for the corresponding norbornanes will be used throughout the remainder of this report to emphasize the close structural relationship between these compounds and norbornene. The numbering is as in **1**.

(3) P. v. R. Schleyer and M. M. Donaldson, *J. Amer. Chem. Soc.*, **78**, 5702 (1956).

(4) K. Alder and G. Stein, *Justus Liebigs Ann. Chem.*, **496**, 204 (1932).

(5) G. Egloff, G. Hulla, and V. I. Kormarewsky, "Isomerization of Pure Hydrocarbons," Reinhold, New York, N. Y., 1942, p 122, and references cited therein.

(6) P. v. R. Schleyer and M. M. Donaldson, *J. Amer. Chem. Soc.*, **82**, 4645 (1960).

(7) P. Wilder and L. Feliu-Otero, *J. Org. Chem.*, **30**, 2560 (1965).

(8) G. L. Bachman, Ph.D. Dissertation, Washington University, St. Louis, Mo., 1964.

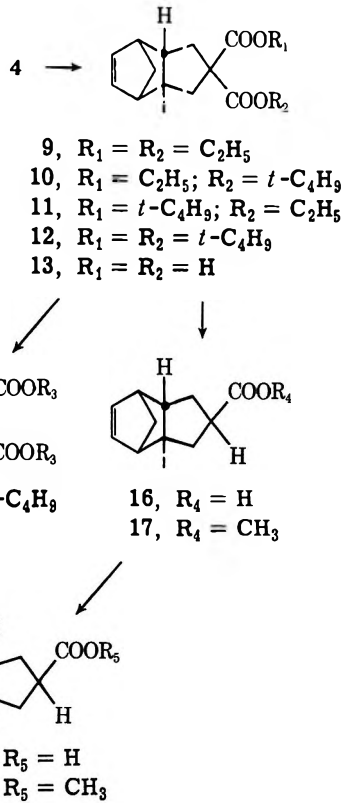
diazonorbornanes, but the structure of this product apparently was not established conclusively.

These results suggested that attachment of a *trans*-5,6-trimethylene bridge to a norbornyl cage was indeed feasible, in spite of the evident increase in strain that this would entail.[6] Although related trans-fused systems have been reported (see discussion below), ring closure to the *trans*-trimethylenenorbornene structure would seem to be especially difficult in view of the anticipated rigidity of the norbornyl cage. Such derivatives would, however, be of considerable interest for defining the limits of the ability of the norbornyl cage to accommodate strain and in studying the effects of strain on this interesting ring structure.

Results and Discussion

Three different approaches to the *trans*-trimethylenenorbornene ring system were investigated. The attempted Thorpe–Ziegler cyclization[9] of the dinitrile **5** and the Dieckmann condensation[9] of the diesters **6** and **7** were unsuccessful, the results in each case (see Experimental Section) indicating that intermolecular reaction remained competitive with intramolecular cyclization even at high dilution and that ring closure was quite slow, as expected. The direct condensation of the ditosylate **4** with diethyl malonate, however, afforded several cyclized products (**9**–**12**) having the trans ring junction (Scheme I). The most efficient

SCHEME I



procedure for effecting this conversion was the slow addition of 2 equiv of potassium *tert*-butoxide to a solution of both reactants in *tert*-butyl alcohol. Although a total reaction time of 1 week was required, the yield of cyclized material was surprisingly high and approached 70%. Because of the extended reaction time, partial ester exchange occurred. The major product of the reaction was the di-*tert*-butyl ester **12**, but the nmr spectrum of the crude product indicated that unexchanged and mixed products (**9**–**11**) were also present. The di-*tert*-butyl ester **12** was readily separable from the mixture by crystallization from ethanol. Separation of the remaining products was not attempted, and the ester mixture was saponified to the common diacid **13**.

The above structural assignments are based on both chemical and spectroscopic evidence. As expected for a substituted malonic acid, the diacid **13** smoothly decarboxylated at elevated temperatures[10] to afford a mixture of isomeric monoacids **16**. The same products were also obtained by decarbalkoxylating the di-*tert*-butyl ester **12** with lithium iodide in collidine[11] and saponifying the intermediate monoesters. Esterification of the acids **16** in methanol then yielded the methyl esters **17**. That this product was a mixture was clearly evident from its nmr spectrum, which contained two methoxyl singlets at 3.77 and 3.65 ppm.

Catalytic hydrogenation of **12**, **13**, or **16** proceeded readily at atmospheric pressure and room temperature with the absorption of 1 equiv of hydrogen to yield the corresponding derivatives of the *trans*-trimethylenenorbornane system (**14**, **15**, and **18**). Esterification of **18** in methanol then yielded the saturated monoester **19**.

In addition to correct elemental analyses for all cyclized products isolated, the neutralization equivalents[12] of the diacid **13** and the monoacid **14** were in satisfactory agreement with those calculated from the indicated formulae. The possibility that a dimeric product has been formed *via* intermolecular condensation was considered unlikely and was excluded by cryoscopic estimation of the molecular weight[12] of the di-*tert*-butyl ester **12**. The value obtained (see Experimental Section) was consistent only with a monomeric product.[13]

Another possibility considered was that of rearrangement during cyclization to afford the isomeric endo,cis or exo,cis products.[10] These structures were, however, clearly excluded by the nmr spectra of the isolated materials. All showed absorptions arising from distinctly nonequivalent vinyl hydrogens, an observation inconsistent with symmetrical structures of the type **1**.

Some insight into the nature of strain effects in the *trans*-trimethylenenorbornene system may be gained by comparison with related systems. Meinwald and coworkers have shown[14] that *trans*-1,2-dibromomethylcylcobutane (**20**) condenses with diethyl malonate to yield derivatives of the strained *trans*-bicyclo[3.2.0]-heptane system (**21**) in good yield. However, the

(9) Both of these procedures have successfully been used in this laboratory for the preparation of the corresponding endo,cis derivatives: (a) R. A. Bell, M. A. Thesis, Bowling Green State University, Bowling Green, Ohio, 1970; (b) Y. K. Chan, M.A. Thesis, Bowling Green State University, Bowling Green, Ohio, 1971.

(10) C. F. Culberson and P. Wilder, *J. Org. Chem.*, **26**, 4289 (1951).

(11) F. Elsinger, *Org. Syn.*, **45**, 7 (1965).

(12) N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," 2nd ed, Interscience, New York, N. Y., 1958.

(13) This determination has been subsequently confirmed by mass spectrometric measurement. The authors are indebted to Ms. W. V. Jones and the Department of Chemistry, Iowa State University, for this analysis.

(14) (a) J. Meinwald, J. J. Turariello, and J. J. Hurst, *J. Org. Chem.*, **29**, 2914 (1964); (b) J. Meinwald, P. Anderson, and J. J. Tufariello, *J. Amer. Chem. Soc.*, **88**, 1301 (1966).

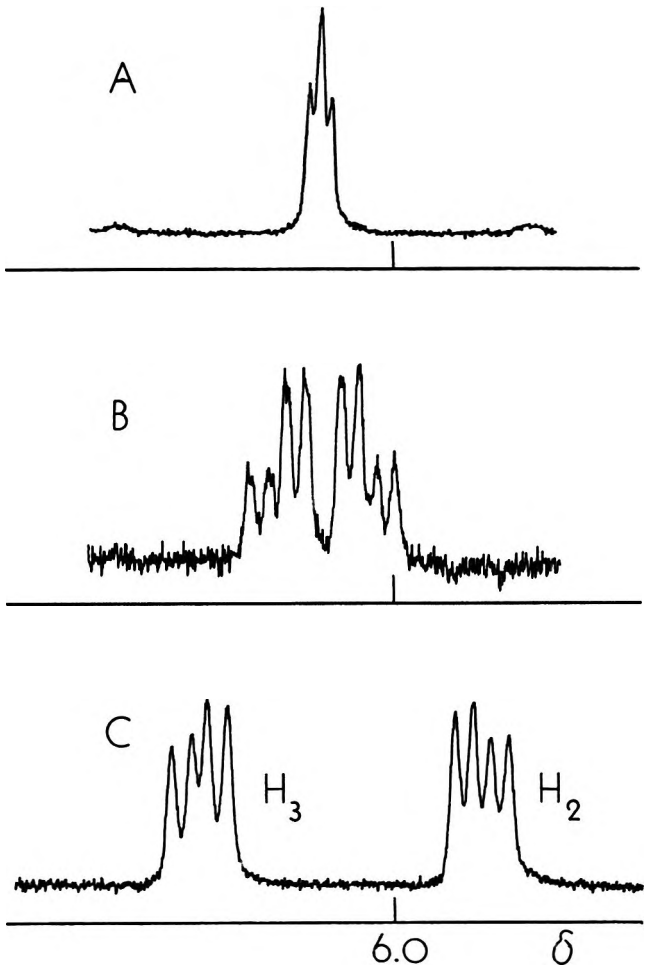
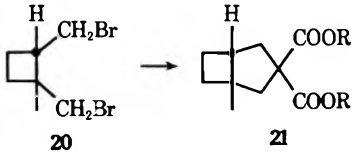


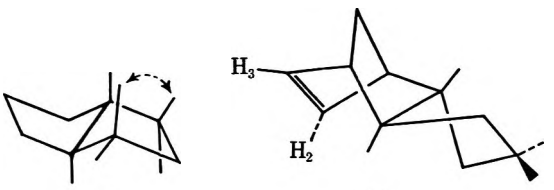
Figure 1.—60-MHz nmr spectra of the vinyl hydrogen region of (a) *endo,cis*-5,6-dicarbethoxymethyl-2-norbornene in $CDCl_3$; (b) **8** in $CDCl_3$; (c) **17**, neat.

puckering of the cyclobutane ring[15] in **20** permits a significant reduction of the dihedral angle between the two groups that must be joined, thus facilitating an otherwise very difficult ring closure. An equal reduction of the dihedral angle in the ditosylate **4** would not be anticipated (see below), and, in fact, cyclization appears to take place less readily than in the case of **20**.



20 **21**

The *trans*-trimethylenenorbornenes may also be viewed as derivatives of the *trans*-bicyclo[3.3.0]octane (*trans*-pentalane) system (**22**) in which positions 2 and 4 are joined by an ethynyl bridge. The *trans*-pentalane system is reported[16] to be about 6 kcal/mol less stable than the cis. This value may, however, be taken as a lower limit for the difference in strain between the *trans*-trimethylenenorbornenes and their cis counterparts (**1**), because the ethynyl bridge in the former requires a considerable twisting of the *trans*-pentalane moiety (**23**) that is not present in the parent trans system **22**.[17] It may thus be concluded that significant strain is introduced into the molecule on cyclization of **4**.



22 **23**

In contrast to this conclusion, neither the olefin stretching frequencies nor the vinyl coupling constants (J_{23}) of the cyclized products obtained in the present study showed evidence[18-20] of an increase in internal strain, the values observed (see Experimental Section) being essentially identical with those reported[18,21] for norbornene itself.[22] It therefore appeared that the strain associated with the *trans*-trimethylene bridge was not effectively transmitted through the norbornyl cage to the 2,3 double bond.

However, a large increase in the separation of the vinyl hydrogen resonances was found in the nmr spectra of these compounds compared to that observed for related disubstituted norbornenes (see Figure 1).[23] That this shift was not the result of substituent effects was evident from the fact that these signals were found at exactly the same positions regardless of the nature of the substituents at position nine. It was therefore concluded that the effect was a characteristic of the ring structure itself.

Wiberg and Nist[19] have observed large downfield shifts of vinyl hydrogen absorptions with increasing bond angle compression in cyclic olefins. In the present system attachment of the *trans*-trimethylene bridge causes a severe twisting of the norbornyl portion of the molecule (**23**). As a result, the $C_2{=}C_3{-}C_4$ bond angle is slightly compressed and the $C_1{-}C_2{=}C_3$ angle is slightly expanded.[24] In norbornene the corresponding angles are equal and are compressed to about 109°.[25,26] Further compression of the $C_2{=}C_3{-}C_4$ angle by the *trans*-trimethylene bridge would then produce the observed downfield shift of the H_3 resonance, while expansion of the $C_1{-}C_2{=}C_3$ angle would produce the shift of the H_2 resonance in the opposite direction. Since these bond angle deformations are mutually compensating, the overall strain applied to the double bond is essentially unchanged, a conclusion consistent

(15) J. B. Lambert and J. D. Roberts, *J. Amer. Chem. Soc.*, **87**, 3884 (1965).

(16) J. W. Barrett and R. P. Linstead, *J. Chem. Soc.*, 611 (1936).

(17) An additional factor involved here is that the *endo*-dicyclopentadienes are approximately 3 kcal/mol less stable than the exo isomers (see ref 6 and references cited therein).

(18) (a) P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **80**, 1700 (1958); (b) R. C. Lord and R. W. Walker, *ibid.*, **76**, 2518 (1954).

(19) K. B. Wiberg and B. J. Nist, *ibid.*, **83**, 1226 (1961).

(20) (a) O. L. Chapman, *ibid.*, **85**, 2014 (1963); (b) G. V. Smith and H. Kriloff, *ibid.*, **85**, 2016 (1963); (c) P. Laszlo and P. v. R. Schleyer, *ibid.*, **85**, 2017 (1963).

(21) P. Laszlo and P. v. R. Schleyer, *ibid.*, **86**, 1171 (1964).

(22) For norbornene these values are as follows: $\nu_{C=C}$ 1568 cm^{-1} (ref 18); J_{23} = 5.80 Hz (ref 20).

(23) The sulfide **2** exhibited similar shifts of the vinyl hydrogen absorptions. The authors are indebted to Mr. D. M. Jacobson for preparing a sample of this compound and obtaining its nmr spectrum.

(24) The remaining bond angles of the norbornyl cage are distorted accordingly.

(25) W. G. Woods, R. Carboni, and J. D. Roberts, *J. Amer. Chem. Soc.*, **78**, 5653 (1956).

(26) The bond angles of **8** and *endo,cis*-5,6-dicarbethoxymethyl-2-norbornene are assumed to be the same as those of norbornene (see ref 28).

with the infrared and coupling constant data presented above.[27]

Similar twisted conformations resulting from nonbonded repulsions have been observed in certain substituted norbornanes.[28] In at least one case a torsional angle about the 2,3 bond as large as 9° was observed in a trans 2,3-disubstituted derivative. Such deformations were not found in substituted norbornenes, and, indeed, they would be less likely because of the restricted rotation about the double bond.[29] Nonetheless, the cylization of the ditosylate **4** and the stability of the products thus formed[30] reveal a surprising capacity on the part of the norbornene ring system to minimize internal strain. It is evident that the geometric requirements of the *trans*-trimethylene bridge in the compounds reported here are satisfied only by a considerable distortion of the norbornenyl cage even at relatively remote positions in the molecule. Because of their greater flexibility, the corresponding saturated compounds would be expected to show even greater deviations from normal geometry. We are currently attempting to define more precisely the limits of the conformational mobility of the norbornene and norbornane ring systems.

Experimental Section

General.—Infrared spectra were obtained using a Perkin-Elmer Model 337 recording spectrophotometer. Nuclear magnetic resonance spectra were obtained with a Varian A-60 spectrometer equipped with a Varian Model V-6058A spin decoupler and a Varian Model V-6057 variable temperature accessory. Chemical shifts (δ) are reported downfield relative to tetramethylsilane as internal reference in the indicated solvents. Coupling constants (J) are reported in hertz. All melting points and boiling points are uncorrected. Microanalyses are by M-H-W Laboratories, Garden City, Mich.

***trans*-5,6-Dicyanomethyl-2-norbornene (5).**—An adaptation of the method of Smiley and Arnold[31] was used for the preparation of this compound. A slurry of 10.8 g (0.22 mol) of sodium cyanide in 100 ml of dimethyl sulfoxide was heated over steam, and a solution of 25.0 g (0.054 mol) of the *trans*-ditosylate **4**[32] in 200 ml of dimethyl sulfoxide was added over 15 min. The resulting mixture was then heated over steam for 19 hr, cooled, and diluted with 50 ml of saturated brine and 50 ml of water. The aqueous mixture was extracted with chloroform, and the combined organic extracts were washed five times with water, dried ($MgSO_4$), and concentrated to afford 10.4 g (110%) of a yellow liquid. This material was fractionated at reduced pressure, and after a forerun of dimethyl sulfoxide the trans dinitrile **5** was collected as a colorless oil (8.6 g, 92%) which crystallized slowly on cooling: bp 126–130° (0.3 mm); mp 37.5–38.5°; ir (neat) 2240 (CN), 1590 cm^{-1} (C=C); nmr ($CDCl_3$) δ 6.37 (d, d, 1, J = 6 and 3 Hz, HC=C), 6.15 (d, d, 1, J = 6 and 3 Hz, C=CH).

Anal. Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.73; H, 7.07; N, 16.41.

***trans*-5,6-Dicarboxymethyl-2-norbornene (6).**—A mixture of 41.0 g (0.20 mol) of the trans dinitrile **5** and 55 g of potassium hydroxide in 125 ml of water was refluxed until the evolution of ammonia ceased (*ca.* 45 hr). The solution was then cooled and extracted with ether (no residue on concentration). The aqueous phase was acidified with concentrated hydrochloric acid, and the resulting white solid precipitate was extracted into ether. The combined ether extracts were washed with saturated brine, dried ($MgSO_4$), and concentrated to yield 33.0 g (80%) of the crude acid **6**, which was recrystallized from ethyl acetate to afford 27.3 g (62%) of the pure product as white needles: mp 155–160°; ir (Nujol) 3350–2500 (OH), 1720 cm^{-1} (C=O); nmr (acetone-d_6) δ 5.67 (d, d, 1, J = 6 and 3 Hz, HC=C), 5.48 (d, d, 1, J = 6 and 3 Hz, C=CH), 5.25 (s, 2, COOH).

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.68; H, 6.61.

***trans*-5,6-Dicarbethoxymethyl-2-norbornene (8).**—A solution of 27.3 g (0.13 mol) of the trans diacid **6** and 1.0 g of *p*-toluenesulfonic acid in 950 ml of ethanol was refluxed for 20 hr. Sodium acetate (1.0 g) was added, and the bulk of the solvent was removed by distillation at reduced pressure. The residue was taken up in ether and was washed with water, saturated sodium bicarbonate, and saturated brine. The resulting ether solution was dried ($MgSO_4$) and concentrated to afford the crude diethyl ester **8** as a yellow oil. This material was fractionated at reduced pressure, and after a small forerun the pure product was collected as a colorless oil (29.5 g, 85%): bp 120–128° (0.6 mm); ir (neat) 1750 (C=O), 1590 cm^{-1} (C=C); nmr ($CDCl_3$) δ 6.27 (d, d, 1, J = 6 and 3 Hz, HC=C), 6.08 (d, d, 1, J = 6 and 3 Hz, C=CH), 4.32 (q, 2, J = 7 Hz, OCH_2CH_3), 4.30 (q, 2, J = 7 Hz, OCH_2CH_3), 1.25 (t, 6, J = 7 Hz, OCH_2CH_3).

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.45; H, 8.27.

***trans*-5,6-Dicarbomethoxymethyl-2-norbornene (7).**—A solution of 6.65 g (0.025 mol) of the trans diethyl ester **8** and 0.5 g of *p*-toluenesulfonic acid in 350 ml of methanol was refluxed for 68 hr. Sodium acetate (0.5 g) was added, and the solvent was removed by distillation at atmospheric pressure. The residue was taken up in ether and was washed with saturated aqueous sodium bicarbonate and saturated brine. The resulting ether solution was dried ($MgSO_4$) and concentrated to afford 6.20 g of crude product. This material was distilled at reduced pressure to yield 3.80 g (54%) of the pure dimethyl ester **7** as a colorless oil: bp 107–108° (3.0 mm); ir (neat) 1750 (C=O), 1580 cm^{-1} (C=C); nmr ($CDCl_3$) δ 6.28 (d, d, 1, J = 6 and 3 Hz, HC=C), 6.13 (d, d, 1, J = 6 and 3 Hz, C=CH), 3.66 (s, 3, OCH_3), 3.65 (s, 3, OCH_3).

Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.26; H, 7.55.

Attempted Thorpe–Ziegler Cyclization of the Dinitrile 5. Method A.—The procedure of Bloomfield and Fennessy[33] was modified as follows. A slurry of 1.5 g (0.03 mol) of sodium cyanide in 30 ml of dimethyl sulfoxide was heated over steam, and 4.6 g (0.01 mol) of the trans ditosylate **4** was added over 0.5 hr. The mixture was stirred over steam for 3.0 hr, and 0.48 g of a 50% dispersion of sodium hydride in mineral oil (0.01 mol NaH) was added rapidly. Heating was continued for 70 hr, and the resulting mixture was poured onto ice. The mixture was extracted with ether, and the combined organic extracts were washed five times with water, dried ($MgSO_4$), and concentrated to yield 0.35 g of a mixture of the starting dinitrile **5** and dimethyl sulfoxide identified by its nmr spectrum.

Method B.[34]—A mixture of 172 mg (1 mmol) of the dinitrile **5** and 48 mg of a 50% dispersion of sodium hydride in mineral oil (1 mmol of hydride) was heated at 130° for 90 hr. The mixture was then cooled and diluted with 15 ml of saturated brine. The aqueous mixture was treated with ether, and a brown solid that precipitated at the interface was collected. This material was dried to yield 149 mg (81%) of a brown solid: mp 145° dec; ir (KBr) 3456 and 3345 (NH_2), 3046 (vinyl H), 2245 (isolated C≡N), 2190 (conjugated C≡N), 1680, 1614, 1541 cm^{-1}; nmr ($CDCl_3$) δ 6.30 (d, d, vinyl H), 6.08 (d, d, vinyl H). The alkaline aqueous layer obtained above was acidified with concentrated hydrochloric acid and extracted with

(27) That the vinyl coupling constant is not altered by these bond angle changes follows from the theoretical conclusion of Karplus that the coupling constant across a cis ethylenic system should depend on the sum of the HC=C bond angle deformations for most dihedral angles. Since in the present system these angles would change in the opposite directions, the effects would again tend to cancel. See M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963). We are investigating this point further.

(28) C. Altona and M. Sundaralinam, *ibid.*, **92**, 1995 (1970).

(29) Dreiding molecular models clearly reveal the greater mobility of the saturated system.

(30) As indicated, for instance, by the fact that the diacid **13** may be decarboxylated at 185° without noticeable loss due to rearrangement or decomposition.

(31) R. A. Smiley and C. Arnold, *J. Org. Chem.*, **25**, 257 (1960).

(32) For the sequence of reactions used to prepare this compound, see (a) O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, **460**, 98 (1928); (b) M. S. Morgan, R. S. Tipson, A. Lowy, and W. E. Baldwin, *J. Amer. Chem. Soc.*, **66**, 404 (1944); (c) L. Baur and C. Nambury, *J. Org. Chem.*, **26**, 1106 (1961); (d) K. Alder and W. Roth, *Ber.*, **87**, 161 (1954).

(33) J. J. Bloomfield and P. V. Fennessey, *Tetrahedron Lett.*, 2273 (1964).

(34) The authors are indebted to Mr. Richard L. Hutchens for carrying out this reaction and obtaining the infrared spectrum of the product.

ether. No residue was obtained on concentration of this extract.

Attempted Dieckmann Cyclization of the Trans Diesters 7 and 8.—Of the several procedures used in attempts to cyclize these two compounds, the following modification of the method of Linstead and Meade[35] is representative. A mixture of 0.71 g (0.003 mol) of the trans dimethyl ester **7**, 0.11 g (0.005 g-atom) of sodium, and one drop of ethanol in 5 ml of xylene was refluxed under dry nitrogen for 16 hr. The resulting mixture was taken up in ether and saturated brine and made acid to litmus with concentrated hydrochloric acid. The organic layer was extracted with 5% sodium hydroxide. No residue was found on concentration of the ether solution. The combined alkaline extracts were acidified with concentrated hydrochloric acid and extracted with ether. The combined ether extracts were washed with saturated brine, dried ($MgSO_4$), and concentrated to yield 0.62 g (98%) of the crude trans diacid **6** identified by its nmr spectrum.

9,9-Dicarbo-*tert*-butoxy-*trans*-5,6-trimethylene-2-norbornene (12) and 9,9-Dicarboxy-*trans*-5,6-trimethylene-2-norbornene (13).—A solution of 3.9 g (0.10 g-atom) of potassium in 200 ml of *tert*-butyl alcohol was added over 10.0 hr to a solution of 46.2 g (0.10 mol) of the trans ditosylate **4** and 16.0 g (0.10 mol) of diethyl malonate in 300 ml of *tert*-butyl alcohol refluxed under dry nitrogen. The resulting mixture was refluxed for 12.0 hr, and a solution of 5.8 g (0.15 g-atom) of potassium in 200 ml of *tert*-butyl alcohol was added over 12 hr. Reflux was then continued for 5 days, and the mixture was poured onto 750 ml of saturated aqueous sodium chloride (brine) and extracted with four 100-ml portions of ether. The combined extracts were washed once with saturated brine, once with 10% hydrochloric acid, once with saturated aqueous sodium bicarbonate, and finally once with saturated brine. The ethereal solution was dried ($MgSO_4$) and concentrated to yield 30.9 g of a pale yellow, semisolid mixture of the esters **9–12**. Crystallization from ethanol afforded 13.6 g (41%) of the di-*tert*-butyl ester **12** as white needles: mp 166–167°; ir (KBr) 3053 (C=CH), 1721 (CO), 1399 and 1371 (C_4H_9), 749 cm^{-1} (C=CH); nmr ($CDCl_3$) δ 6.58 (d, d, 1, J = 6 and 3 Hz, vinyl H), 5.82 (d, d, 1, J = 6 and 3 Hz, vinyl H), 1.47 (s, 9, C_4H_9), 1.45 (s, 9, C_4H_9).

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04; mol wt, 334. Found: C, 71.97; H, 8.84; mol wt,[12,13] 329.

The combined mother liquors of the above crystallization were concentrated and treated with 3.5 g of potassium hydroxide in 50 ml of water, and the mixture was refluxed for 12.0 hr. The resulting solution was washed once with chloroform (no residue on concentration), and the aqueous layer was made acid to litmus with concentrated hydrochloric acid. The precipitated solid was extracted into chloroform, and the organic phase was washed with saturated brine, dried ($MgSO_4$), and concentrated to yield 5.6 g (25%) of the diacid **13** as a white solid. A small portion of this material was recrystallized from ethyl acetate for analysis: mp 211–212°; ir (KBr) 3350–2300 (OH), 1704 (C=O), 1568 (C=C), 952 (OH), 745 cm^{-1} (vinyl H); nmr (acetone-d_6) δ 8.33 (s, 2, OH), 6.57 (d, d, 1, J = 5.5 and 3 Hz, vinyl H), 5.82 (d, d, 1, J = 5.5 and 3 Hz, vinyl H).

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35; neut equiv, 111. Found: C, 64.99; H, 6.43; neut equiv,[12] 115.

9-Carboxy-*trans*-5,6-trimethylene-2-norbornene (16). Method A.—A procedure similar to that of Culberson and Wilder[10] for a similar reaction was used for the decarboxylation of the diacid **13**. A mixture of 3.0 g (0.014 mol) of **13** and 50 ml of phenyl ether was immersed in an oil bath preheated to 135°, and the bath temperature was slowly raised to a maximum of 185° over 0.5 hr, by which time the evolution of carbon dioxide had ceased. The resulting solution was cooled, diluted with 100 ml of ether, and extracted with two 20-ml portions of 5% aqueous sodium hydroxide. The combined alkaline extracts were washed once with ether (no residue on concentration) and acidified with 20 ml of 10% hydrochloric acid. The precipitated solid was taken up in ether, and the ethereal solution was washed with saturated brine, dried ($MgSO_4$), and concentrated to afford the monoacid mixture **16**. This material was sublimed at reduced pressure (1.0 mm at 100°) to afford the pure product as white needles (2.0 g, 83%): mp 69°; ir (KBr) 3053 (vinyl H), 3200–2400 (OH), 1714 (C=O), 1567 (C=C), 898 (OH), 720 cm^{-1} (vinyl H); nmr ($CDCl_3$) δ 10.88 (s, 1, OH), 6.57 (d, d, 1, J = 5.5 and 3 Hz, vinyl H), 5.82 (d, d, 1, J = 5.5 and 3 Hz, vinyl H).

(35) R. P. Linstead and E. M. Meade, *J. Chem. Soc.*, 940 (1934).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92; neut equiv, 178. Found: C, 74.29; H, 7.98; neut equiv,[12] 173.

Method B.[11]—A solution of 6.7 g (0.02 mol) of the di-*tert*-butyl ester **12** in 50 ml of collidine was added to a solution of 11.3 g (0.06 mol) of lithium iodide trihydrate in 15 ml of collidine, and the mixture was refluxed for 24 hr. The reaction mixture was then poured onto ice and made acid to litmus with concentrated hydrochloric acid. The aqueous solution was extracted with ether, and the combined extracts were washed with 10% hydrochloric acid, 10% sodium bisulfite, and saturated brine. The crude product was extracted with three 10-ml portions of 5% sodium hydroxide, and the extracts were combined and retained (solution A). The ether phase was dried ($MgSO_4$) and concentrated to afford 2.5 g of a red-black oil. This material was dissolved in 25 ml of ethanol and 5 ml of water, and 5 g of sodium hydroxide was added. The solution was then refluxed for 24 hr and diluted with 50 ml of saturated brine. The aqueous solution was washed with ether (no residue on concentration) and made acid to litmus with concentrated hydrochloric acid. The precipitated solid was taken up in ether, and the ether solution was washed with saturated brine, dried ($MgSO_4$), and concentrated to yield 1.5 g (42%) of a black oil. Sublimation of this material at reduced pressure afforded the monoacids **16** as white needles, mp 59–60°. The nuclear magnetic resonance spectrum of this product was identical with that of the product obtained by the thermal decarboxylation of the diacid **13**.

The combined alkaline extracts obtained above (solution A) were acidified with concentrated hydrochloric acid, and the precipitated solid was extracted into ether. The ether solution was washed with saturated brine, dried ($MgSO_4$), and concentrated to give 2.0 g (45%) of the diacid **13**, identified by its nuclear magnetic resonance spectrum.

9-Carbomethoxy-*trans*-5,6-trimethylene-2-norbornene (17).—A solution of 360 mg (2.0 mmol) of the monoacids **16** and 36 mg of *p*-toluenesulfonic acid in 30 ml of methanol was stirred at room temperature for 16 hr. Sodium acetate (100 mg) was added, and the bulk of the solvent was distilled. The residue was diluted with an equal volume of saturated brine and extracted with ether. The combined ether extracts were washed with saturated brine and saturated sodium bicarbonate, and were dried ($MgSO_4$) and concentrated to afford 423 mg of a yellow oil. This material was evaporatively distilled at reduced pressure to yield the methyl esters **17** as a colorless oil (285 mg, 74%): ir (neat) 3049 (vinyl H), 1734 (C=O), 1567 cm^{-1} (C=C); nmr ($CDCl_3$) δ 6.57 (d, d, 1, J = 5.75 and 3.35 Hz, H_3), 5.82 (d, d, 1, J = 5.75 and 2.85 Hz, H_2), 3.67 (s, OCH_3), 3.65 (s, OCH_3), 3.20 (m, H_9), 2.72 (m, H_1), and 2.52 (m, H_4).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.88; H, 8.49.

9-Carboxy-*trans*-5,6-trimethylenenorbornane (18).—To a solution of 2.41 g (0.014 mol) of unsaturated acid **16** in 30 ml of ethyl acetate a few milligrams of 30% palladium on carbon was added, and the mixture was subjected to hydrogen at atmospheric pressure and room temperature until the absorption of hydrogen ceased. A total volume of 307 ml of hydrogen was taken up (theoretical, 302 ml). The catalyst was removed by filtration, and the filtrate was concentrated at reduced pressure to afford 2.1 g (87%) of the saturated acid **18**. Sublimation of this material at reduced pressure yielded the pure product: mp 45–47°; ir (KBr) 2850–2450 (COOH), 1700 cm^{-1} (C=O).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.41; H, 9.01.

9,9-Dicarbo-*tert*-butoxy-*trans*-5,6-trimethylenenorbornane (14).—The diester **12** was hydrogenated by the same procedure used for the hydrogenation of **16**. The saturated diester **14** was obtained as white needles from ethyl acetate in 70% yield: mp 123–125°; ir (KBr) 1700 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.45 (s, 9, t-C_4H_9).

Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.41; H, 9.58.

9,9-Dicarboxy-*trans*-5,6-trimethylenenorbornane (15).—This compound was obtained from the unsaturated diacid **13** by the hydrogenation procedure described above. The product **15** was obtained in 80% yield as white needles from ethyl acetate: mp 214–215°; ir (KBr) 3200–2900 (COOH), 1700 cm^{-1} (C=O); nmr (acetone-d_6) δ 7.58 (s, 1, COOH).

Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.48; H, 7.32.

9-Carbomethoxy-*trans*-5,6-trimethylenenorbornane (19).—The saturated acid **18** was esterified in methanol by the same procedure used for the preparation of the ester **17**. The product **19** was obtained in 89% yield as a colorless oil: bp 126–127°; ir (neat) 1750 cm^{-1} (C=O); nmr ($CDCl_3$) δ 3.68 (s, 3, OCH_3).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.17; H, 9.35. Found: C, 74.18; H, 9.51.

Registry No.—**5**, 34561-91-6; **6**, 34561-92-7; **7**, 34561-93-8; **8**, 34561-94-9; **12**, 34561-95-0; **13**, 34561-96-1; **14**, 34561-97-2; **15**, 34561-98-3; **16** isomer a, 34599-26-3; **16** isomer b, 34599-27-4; **17** isomer a, 34561-99-4; **17** isomer b, 34562-00-0; **18** isomer a, 34562-01-1; **18** isomer b, 34562-02-2; **19** isomer a, 34562-03-3; **19** isomer b, 34562-04-4.

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Studies on Reactions of Isoprenoids. XVII.[1] The Cycloaddition Reactions of Norbornadiene with Some Unsymmetrically Substituted Dienophiles. Competitive Ionic Additions with Homo-Diels–Alder Reactions

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The reactions of norbornadiene (1) with unsymmetrically substituted acetylenic and heterodienophiles were investigated. Cyanoacetylene and *N-tert*-butylpropiolamide as acetylenic dienophiles gave only homo-Diels–Alder adducts **3a** and **3b**, respectively, while chlorocyanoacetylene afforded 2 + 2 cycloadduct **4** and its skeletal rearrangement product **5** *via* an ionic intermediate **7** together with homo-Diels–Alder adduct **3c**. Phenylacetylene, chloropropiolamide, and dimethylaminocyanoacetylene did not afford any isolable adducts. The reaction of **1** with methylenebisurethane in the presence of boron trifluoride etherate afforded 8-aza-δ-cyclane (**10**) and the 3-aminonortricyclene derivative **11**, while that with benzalbisurethane gave only 3-nortricyclylurethane (**12**). Anhydrochloralurethane did not afford any adduct.

We have previously reported 1,4-cycloaddition reactions of some monoterpenoid diene and triene systems.[1,2] As an extension of these studies, this paper deals with cycloaddition of homoconjugated norbornadiene (**1**) and unsymmetrically substituted acetylenic and heterodienophiles. It is well known that **1** gives δ-cyclane derivatives *via* the homo-Diels–Alder ($_\pi2_s + _\pi2_s + _\pi2_s$ cycloaddition) reaction,[3,4] and quadricyclane (**6**) affords tricyclo[4.2.1.$0^{2,5}$]non-7-ene derivatives *via* the bishomodiene addition ($_\pi2_s + _\sigma2_a + _\sigma2_a$ cycloaddition)[5] as the thermally allowed process under the Woodward–Hoffmann orbital symmetry rules.[6] However, only reactions of **1** with symmetrically substituted active acetylenes such as dimethyl acetylenedicarboxylate and dicyanoacetylene seem to have been studied.[4] In order to know the chemical behavior of the homoconjugated diene system of **1** with dienophiles that are strongly perturbed by substituents, we have investigated the reactions of **1** with cyanoacetylene (**2a**), *N-tert*-butylpropiolamide (**2b**), chlorocyanoacetylene (**2c**), phenylacetylene (**2d**), chloropropiolamide (**2e**), and dimethylaminocyanoacetylene (**2f**) as well as those with the heterodienophiles *N*-ethoxycarbonylimines **9a**, **9b**, and **9c**.

Results and Discussion

An equimolar mixture of **1** and **2a** was heated under the conditions shown in Table I. The product **3a** was isolated as a colorless liquid by distillation. The best yield was obtained by heating the reactants without solvent or any addenda at 145–160°, while the presence of aluminum chloride or copper(II) bromide lowered the yields considerably.[7,8]

TABLE I
THE YIELD OF **3a** UNDER VARIOUS CONDITIONS

Solvent	Addenda	Temp, °C	Time, hr	Yield,[a] %
None	None	160	28	31
None	None	145	40	31
Benzene	None	90	69	26
None	$AlCl_3$[b]	80	70	9
Benzene	$CuBr_2$[b]	80	240	Trace

[a] Isolated yield. [b] Trace–0.3 molar equiv amounts were examined but the results were similar.

The structure of **3a** was determined as 8-cyano-δ-cyclene (8-cyanotetracyclo[4.3.0.0.^{2,4}0^{3,7}]non-8-ene)[9] on the basis of analytical and spectral data. The nmr spectrum (CCl_4, 60 MHz) revealed a doublet at τ 3.15

(1) Part XVI: T. Sasaki, S. Eguchi, and H. Yamada, *Tetrahedron*, **27**, 4511 (1971).

(2) (a) T. Sasaki, S. Eguchi, and T. Ishii, *J. Org. Chem.*, **34**, 3749 (1969); (b) T. Sasaki, S. Eguchi, T. Ishii, and H. Yamada, *ibid.*, **35**, 4273 (1970); (c) T. Sasaki, S. Eguchi, and H. Yamada, *ibid.*, **36**, 1584 (1971).

(3) For olefinic and heterodienophiles, see E. F. Ullmann, *Chem. Ind. (London)*, 1173 (1958); R. C. Cookson, J. Dance, and J. Hudec, *J. Chem. Soc.*, 5416 (1964); J. J. Tufariello, T. F. Mich, and P. S. Miller, *Tetrahedron Lett.*, 2293 (1966); see also ref 6.

(4) For symmetrical acetylenic dienophiles, see R. C. Cookson and J. Dance, *ibid.*, 879 (1962); C. F. Huebner, E. Donoghue, L. Dorfman, E. A. Stuber, N. Danieli, and E. Wenkert, *ibid.*, 1185 (1966).

(5) C. D. Smith, *J. Amer. Chem. Soc.*, **88**, 4273 (1966); G. Kaupp and H. Prinzbach, *Chem. Ber.*, **104**, 182 (1971).

(6) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 827 (1969).

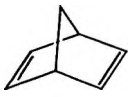
(7) For the catalytic action of aluminum chloride on 1,4 cycloadditions, see P. Yates and F. Eaton, *J. Amer. Chem. Soc.*, **82**, 4436 (1960); T. Inukai and T. Kojima, *J. Org. Chem.*, **31**, 2032 (1966), and references cited therein.

(8) For the formation of norbornadiene di[copper(I) bromide] from **1** and copper(II) bromide, see W. C. Baird, Jr., and J. H. Surridge, *ibid.*, **35**, 2090 (1970).

(9) For the nomenclature, see footnote 3 in P. K. Freeman, D. M. Balls, and J. N. Blazevich, *J. Amer. Chem. Soc.*, **92**, 2051 (1970).

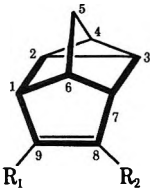
due to the C-9 vinyl proton and two characteristic multiplets at τ 8.18 and 8.53 due to C_4 H and C_2 and C_3 cyclopropyl methine protons supporting the assigned structure (Scheme I).

SCHEME I



1 + $R_1C{\equiv}CR_2$ →

2a, R_1 = H; R_2 = CN
b, R_1 = H; R_2 = CONH-*t*-Bu
c, R_1 = Cl; R_2 = CN
d, R_1 = H; R_2 = C_6H_5
e, R_1 = Cl; R_2 = $CONH_2$
f, R_1 = NMe_2; R_2 = CN



3a, R_1 = H; R_2 = CN
b, R_1 = H; R_2 = CONH-*t*-Bu
c, R_1 = Cl; R_2 = CN

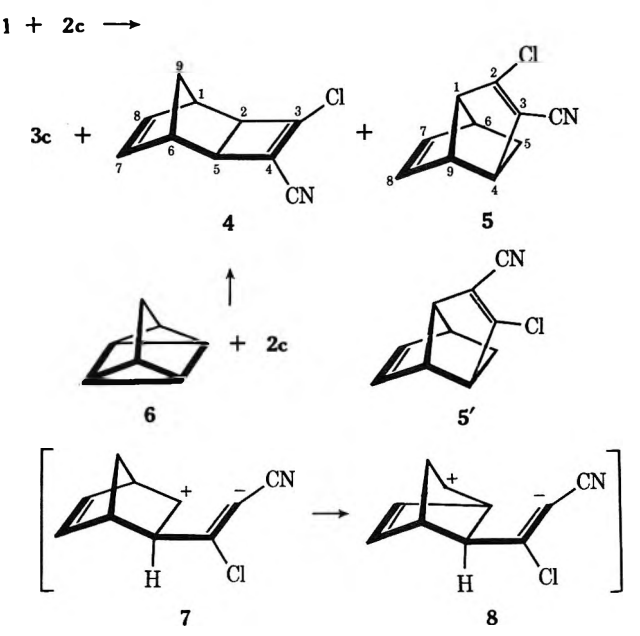
The reaction of **1** with **2b** at 165° for 100 hr afforded also 8-*N*-*tert*-butylcarbamoyl-δ-cyclene (**3b**) in very low yield, but no other isolable products were obtained (Scheme I).

In contrast to the behavior of **2a** and **2b**, chlorocyanoacetylene (**2c**) reacted with **1** under milder conditions (80° for 30 hr). Unexpectedly, at least four products were produced in a 60:10:30:<1 ratio on vpc analysis. The major products **3c**, **4**, and **5** were isolated in 40, 6, and 20% yields, respectively, by preparative vpc. All of these products were 1:1 adducts from analytical and mass spectral data. The mass spectra showed M^+ and M + 2 ion peaks at *m/e* 177 and 179 in 3:1 ratio, supporting the molecular formula of $C_{10}H_8NCl$. The presence of a cyano group in **3c**, **4**, and **5** was demonstrated by ir absorptions at 2250, 2260, and 2300 cm^{-1}, respectively. Compound **3c** was shown to be 8-cyano-9-chloro-δ-cyclene, a homo-Diels–Alder adduct by its characteristic nmr signals ($CDCl_3$) at τ 7.08 and 7.20 (broad s, C_1 and C_7 H), 7.65 (broad s, C_6 H), 8.10 (m, C_4 H), 8.35 (m, C_2 and C_3 H), and 8.38 (t, J = 1 Hz, C_5 methylene protons).

Compound **4** was determined to be *exo*-3-cyano-4-chlorotricyclo[4.2.1.$0^{2,5}$]nona-3,7-diene, a 2 + 2 adduct, from its characteristic nmr signals at τ 3.82 (m, C_7 and C_8 vinyl protons), 7.28 (broad s, methine protons at C_1, C_2, C_5, and C_6), and 8.45 (broad s, C_9 methylene protons). The assigned structure **4** was verified by an alternative synthesis *via* the bishomodiene type cycloaddition of quadricyclane **6** to **2c** at 80° in benzene.[10]

Compound **5** exhibited two broad singlet signals at τ 3.85 (2) and 6.92 (2) assignable to the C_7 and C_8 vinyl protons and to the C_6 and C_9 bridgehead protons respectively, a pair of double doublets at τ 6.15 and 7.20, and an unsymmetrically split AB type quartet centered at τ 8.15. The latter signals were assignable to the C_1 and C_4 methine protons, and to the C_5 methylene protons (H_n and H_x), respectively, on the basis of the coupling constants ($J_{1,4}$ = 8.0, $J_{1,3}$ = 2.0, $J_{4,Hn}$ = 1.5, $J_{Hn,Hx}$ = 10.2, $J_{Hx,6}$ = 4.5, $J_{Hx,7}$ = 1.5 Hz). Two structures, 2-chloro-3-cyano- (**5**) and 2-cyano-3-chlorotricyclo[4.3.0.$0^{4,9}$]nona-2,7-diene (**5′**) were compatible with the nmr data. However, because nucleophilic addition to **2c** occurs always at the β position of the cyano group,[11] the structure was concluded to be **5** (Scheme II).

SCHEME II



The formation of **4** and **5** suggests that an ionic cycloaddition initiated by an exo approach of **2c** to **1** is competing with the homo-Diels–Alder reaction. The ionic character of the cycloaddition to give **4** and **5** was demonstrated by the solvent effect on the product ratio as summarized in Table II. The formation of **5** was favored in polar acetonitrile, while those of **3c** and **4** was favored in nonpolar benzene. This fact could be explained reasonably by assuming the initial formation of a zwitterionic intermediate **7** or more precisely its homoallylic type equivalent which can cyclize to **4** directly and to **5** after a Wagner–Meerwein rearrangement[12] (Scheme II). The facility of the rearrangement in the polar solvent decreases the yields of **4** and **3c**. The possibility that **3c**, **4**, and **5** interconvert was excluded by the fact that all of these

TABLE II
SOLVENT EFFECT ON THE REACTION OF 1 AND 2c[a]

Solvent	Product ratio, %[b] 3c	4	5	Other[c]
None	60	10	30	<1
Benzene	50	9	38	3
Acetonitrile	26	2	64	8

[a] An equimolar mixture was heated at 80° for 40 hr. [b] Based on vpc analyses. [c] Unidentified.

(10) No other products were detected on vpc analysis in this reaction.

(11) T. Sasaki, A. Kojima, and M. Ohta, *J. Chem. Soc. C*, 196 (1971).

(12) For Wagner–Meerwein rearrangments *via* homoallylic intermediates in electrophilic additions to **1**, see J. A. Berson, "Molecular Rearrangements," Part I, Interscience, New York, N. Y., 1963, p 198.

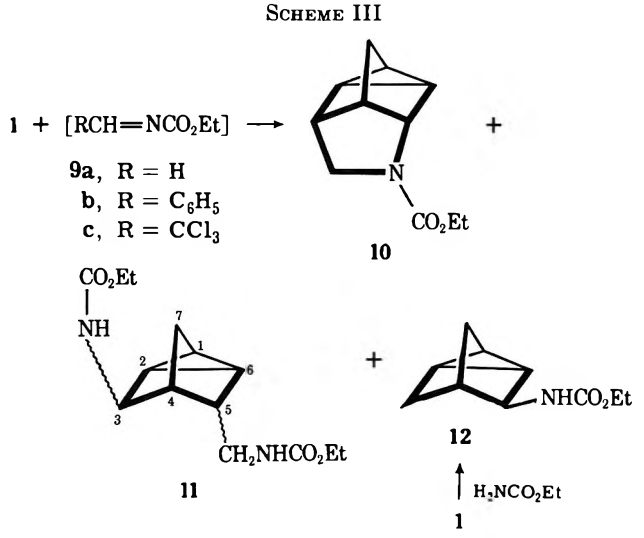
products were stable even on heating at 80° for 40 hr in acetonitrile.

In the reaction of **1** with other unsymmetrical acetylenes such as **2d** (150°, 100 hr), **2e** (90°, 30 hr), and **2f** (80°, 40 hr), no well-defined adducts could be isolated; only intractable side products were produced or unreacted starting materials were recovered.

The reaction of **1** with **9a** was carried out in the usual way by heating a benzene solution of methylenebisurethane in the presence of boron trifluoride etherate.[13] Work-up afforded two major products, **10** and **11**, in 18.5 and 63% yields, respectively. Compound **10** was a 1:1 adduct from its analysis and mass spectrum, M^+ at *m/e* 193, and was deduced to be *N*-ethoxycarbonyl-8-aza-δ-cyclane from the nmr signals at τ 5.90 (unsymmetrical q, J = 7.5 Hz, $CO_2CH_2CH_3$ and C_7 H), 6.52 and 6.72 (AB q, J = 9.0 Hz, C_9 methylene), 7.65 (broad s, C_1 H), 8.08 (broad s, C_6 H), 8.41 (s, C_5 methylene), and 8.75 (unsymmetrical t, J = 7.5 Hz, $CO_2CH_2CH_3$ and cyclopropane ring protons).

Compound **11**, $C_{14}H_{22}O_4N_2$, had a M^+ ion peak at *m/e* 282 in the mass spectrum and nmr signals at τ 5.15 (broad d, J = 5.5 Hz, disappeared on deuteration, two NH), 5.88 (q, J = 7.5 Hz, two $CO_2CH_2CH_3$), 6.40 (d, t, J = 6.5 and 1.5 Hz, broad s on deuteration, C_3 H),[14] 6.92 (t, J = 7.0 Hz, d, J = 7.0 Hz after deuteration, $CHCH_2NH$), 7.85–8.20 (triplet overlapping a broad singlet, J = *ca.* 7 Hz, the triplet being further split into unsymmetrical triplets with J = *ca.* 1 Hz, C_5 H and C_4 H), and 8.4–9.0 (m, overlapping a triplet, J = 7.5 Hz, two $CO_2CH_2CH_3$ and other ring protons). Hence, the structure was assigned as 3-*N*-ethoxycarbonylamino-5-*N*-ethoxycarbonylaminomethyltricyclo-[2.2.1.0^{2,6}]heptane (**11**) (Scheme III). The stereo-

SCHEME III



chemistry at C_5 and C_3 could not be determined, though an exo orientation of the $CH_2NHCO_2CH_2CH_3$ group is logical considering that **11** should be produced by exo addition of **9a** to **1** followed by addition of urethane. **10** is apparently formed *via* an endo approach of **9a** to **1**.

(13) *N*-Ethoxycarbonylimines **9a** and **9b** or their delocalized cations are postulated as the intermediate in the well-known 1,4 cycloadditions of dienes with methylene- and benzalbisurethanes. For a recent review, see H. E. Zaugg, *Synthesis*, 64 (1970).

(14) For nmr data of some nortricyclene derivatives, see B. C. Henshaw, D. W. Rome, and B. L. Johnson, *Tetrahedron*, **27**, 2255 (1971); R. S. Neale and E. B. Whipple, *J. Amer. Chem. Soc.*, **86**, 3130 (1964).

The very low yield of **10** in the above reaction was somewhat improved by using addenda (10 wt %) such as copper(II) chloride and bromide to afford 30 and 51%, and 32 and 46%, yields of **10** and **11**, respectively.

The reaction of **1** with benzalbisurethane under identical conditions resulted in the formation of only **12**, an adduct of urethane to **1**,[15] indicating much less reactivity of **9b** than **9a**. A trace amount of **12** was also produced in the reaction with methylenebisurethane.

Anhydrochloralurethane **9c**[16,17] gave no adducts to **1** on heating at 80° for 6 hr in benzene.

Comparison of the above results with those reported for symmetrical dienophiles is of interest in view of the homo-Diels–Alder reactivity of **1**. The fact that even an acetylenic dienophile like **2c** affords considerable amounts of cycloadducts such as **4** and **5** different from the homo-Diels–Alder adduct suggests that the unsymmetrical nature of the dienophiles is one of the important factors in determining the products, since tetracyanoethylene, a very strong symmetrical dienophile, affords quantitatively the corresponding homo-Diels–Alder adduct with **1**, while competitive 1,2 and 1,4 cycloadditions are well known in the reaction of tetracyanoethylene with dienes.[18,19] Furthermore, in the reaction with cyclopentadiene, **2c** affords the normal 1,4 cycloadduct, 2-cyano-3-chloronorbornadiene, in over 73% yield.[20]

Experimental Section[21]

General Procedure for the Reactions of 1 with Dienophiles.—An equimolar mixture of freshly distilled norbornadiene and a dienophile[22] was heated in a sealed tube under an atmosphere of nitrogen (see Tables I and II).

8-Cyano-δ-cyclene (3a).—This was obtained by distillation under reduced pressure of the crude reaction product from **1** and **2a** as a colorless oil: bp 122–124° (27 mm); n^{19}D 1.5342; ir (neat) 3060 (cyclopropane), 2250 (CN), 1575 and 1460 (norbornene), and 795 cm^{-1} (nortricyclene);[9] uv max (EtOH) 224 nm (ε 7100); nmr (CCl_4) τ 3.15 (d, J = 3.3 Hz, 1, C_9 H), 7.20 (m, 2, C_1 and C_1 H_7), 7.84 (broad s, 1, C_6 H), 8.18 (m, 1, C_4 H), 8.35 (t, J = 1 Hz, 2, C_5 H), and 8.53 (m, 2, C_2 and C_3 H); mass spectrum *m/e* (rel intensity) 143 (84, M^+), 142 (73), 116 (100, M − HCN), 115 (83), and 91 (40).

Anal. Calcd for $C_{10}H_9N$: C, 83.88; H, 6.34; N, 9.78. Found: C, 84.04; H, 6.35; N, 9.61.

8-*N*-*tert*-Butylcarbamoyl-δ-cyclene (3b).—A dark brownish, sticky product obtained from **1** and **2b** was purified on a silica gel column eluting with chloroform–methanol to afford **3b** in 9.3% yield as colorless crystals: mp 152–156°; ir (KBr) 3340, 1630, 1580, 814, and 792 cm^{-1}; uv max (EtOH) 240 nm (ε 3400);

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(17) F. Feist, *Ber.*, **45**, 945 (1912).

(18) A. T. Blomoquist and Y. C. Meinwald, *J. Amer. Chem. Soc.*, **81**, 667 (1959).

(19) For a review, see P. D. Bartlett, *Quart. Rev., Chem. Soc.*, **24**, 473 (1970).

(20) Our unpublished data.

(21) Microanlyses were performed with a Perkin-Elmer 240 elemental analyzer. Melting points were determind with a Yanagimoto hot-stage type melting point apparatus and are corrected. Boiling points are uncorrected. Ir spectra were obtained with a JASCO IR-S spectrometer and uv spectra with a JASCO ORD/UV5 spectrometer. Nmr spectra were taken with a JEOL-C-60HL spectrometer at 60 MHz using TMS as internal standard, and mass spectra with a JEOL-01SG spectrometer at 75 eV. Vpc analyses were performed with a NEVA gas chromatograph Model 1400 and preparative vpc with a Varian Aerograph Model 700 (silicone SE-30).

(22) For cyanoacetylene (**2a**), *N*-*tert*-butylpropiolamide (**2b**), chlorocyanoacetylene (**2c**), and chloropropiolamide (**2e**), see footnotes 18–20 in ref 2a, and for dimethylaminocyanoacetylene (**2f**), see T. Sasaki and A. Kojima, *J. Chem. Soc.*, 476 (1970).

nmr ($CDCl_3$) τ 3.46 (d, J = 3.2 Hz, 1, C_9 H), 4.70 (s, 1, NH), 7.14 and 7.32 (m, 2, C_7 and C_1 H), 7.90 (broad s, 1, C_6 H), 8.22 (m, 1, C_4 H), 8.49 (m, 2, C_2 and C_3 H), and 8.60 (s, 11, C_5 H and CH_3).

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.12; H, 8.83; N, 6.68.

8-Cyano-9-chloro-δ-cyclene (3c), *exo*-3-Cyano-4-chlorotricyclo[4.2.1.0^{2,5}]nona-3,7-diene (4), and 2-Chloro-3-cyanotricyclo[4.3.0.0^{4,9}]nona-2,7-diene (5).—The reaction product of 1 with 2c could not be extensively pruified by a fractional distillation under reduced pressure, and hence preparative vpc separation was performed at 150° on a silicone SE-30 column (20 ft × 0.375 in.). The first peak afforded 4 in 6% yield as a colorless oil which on standing crystallized: mp 36–37°; ir (KBr) 2260 and 1610 cm^{-1}; uv max (EtOH) 228 (infl) and 248 nm (ϵ 1700); mass spectrum m/e (rel intensity) 179 (0.3, M + 2), 177 (1, M$^+$), 142 (16, M − Cl), 115 (46, M − HCN), 66 (57, cyclopentadiene), and 51 (100, cyanoacetylene).

Anal. Calcd for $C_{10}H_8NCl$: C, 67.62; H, 4.54; N, 7.88. Found: C, 67.52; H, 4.67; N, 7.70.

The second peak afforded 3c in 40% yield as colorless crystals: mp 40–42°; ir (KBr) 2250 and 1585 cm^{-1}; uv max (EtOH) 240 nm (ϵ 9100); mass spectrum m/e (rel intensity) 179 (20, M + 2), 177 (61, M$^+$), 142 (99, M − Cl), and 115 (100, M − HCN).

Anal. Calcd for $C_{10}H_8NCl$: C, 67.62; H, 4.54; N, 7.88. Found: C, 67.52; H, 4.67; N, 7.70.

The third peak was very weak and was not resolved well with the fourth peak, and therefore, pure material could not be obtained.

The fourth peak gave 5 in 20% yield as a colorless oil: $n^{16.5}$D 1.5524; ir (neat) 2300 and 737 cm^{-1}; uv max (EtOH) 227 and 238 nm (ϵ 800 and 490); mass spectrum m/e (rel intensity) 179 (0.3, M + 2), 177 (1, M$^+$), 142 (16, M − Cl), 115 (46, M − HCN), 66 (57, cyclopentadiene), and 51 (100, cyanoacetylene).

Anal. Calcd for $C_{10}H_8NCl$: C, 67.62; H, 4.54; N, 7.88. Found: C, 67.85; H, 4.59; N, 7.60.

Reaction of 1 with Methylenebisurethane.—To a refluxing mixture of methylenebisurethane (9.5 g, 0.05 mol) and 47% boron trifluoride etherate (1.81 g) in dry benzene (50 ml) was added a solution of 1 (4.6 g, 0.05 mol) in dry benzene (20 ml) slowly over a period of 3 hr and the mixture was further refluxed for 3 hr. The cooled mixture was washed with water several times and dried over sodium sulfate. Removal of the solvent gave a dark brownish residue (*ca.* 6 g) which was purified on a silica gel column eluting with chloroform–methanol to give ***N*-ethoxycarbonyl-8-aza-δ-cyclane (10)** as a colorless oil. This was also obtained by distillation of the crude product: bp 88–90° (0.4 mm); n^{20}D 1.5179; ir (neat) 1700, 800, and 770 cm^{-1}.

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.40; H, 7.82; N, 7.22.

Further elution gave ***N*-ethoxycarbonylamino-5-*N*-ethoxycarbonylaminomethyltricyclo[2.2.1.0^{2,6}]heptane (11)** as colorless crystals: mp 130–131°; ir (KBr) 3260, 1700, 805, and 782 cm^{-1}.

Anal. Calcd for $C_{14}H_{22}N_2O_4$: C, 59.55; H, 7.85; N, 9.92. Found: C, 59.69; H, 7.84; N, 9.76.

Reaction of 1 with Benzalbisurethane.—The reaction was carried out as above. Work-up afforded only **3-nortricyclylurethane (12)** in *ca.* 50% yield as colorless crystals, mp 61–64° (lit.[15] mp 64°); there was no depression of the mixture melting point with an authentic sample.

Reaction of 1 with Anhydrochloralurethane (9c).—An equimolar mixture of 1 and 9c[16] in dry benzene was heated at 80° for 6 hr. After removal of the solvent, the residue was dissolved in chloroform and was purified on a silica gel column ($CHCl_3$–MeOH). The major product was an adduct of chloralurethane to 9c, which was isolated in 23% yield as needles: mp 164–166° (lit.[17] mp 163–164°); nmr ($CDCl_3$) τ 3.95–4.70 (broad m, 4, two –NHCH), 5.78 (q, 4, two $CO_2CH_2CH_3$), and 8.70 (t, 6, two $CO_2CH_2CH_3$).

Further elution gave only unidentified oily minor products.

Registry No.—**1**, 121-46-0; **2a**, 1070-71-9; **2b**, 22237-84-9; **2c**, 2003-31-8; **2d**, 536-74-3; **2e**, 33064-30-1; **2f**, 28112-07-4; **3a**, 34627-34-4; **3b**, 34627-35-5; **3c**, 34627-36-6; **4**, 34627-45-7; **5**, 34627-37-7; **9a**, 34627-38-8; **9b**, 27593-62-0; **9c**, 16723-30-1; **10**, 34627-41-3; **11**, 34627-42-4.

Palladium-Catalyzed Vinylic Hydrogen Substitution Reactions with Aryl, Benzyl, and Styryl Halides

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Aryl, benzyl, and styryl halides react with olefinic compounds in the presence of a hindered amine and a catalytic amount of palladium metal to form vinylic derivatives in which the aryl, benzyl, or styryl group has replaced a vinylic hydrogen of the original olefin. The reactions occur readily at 100° and yields are generally good.

Mizoroki[1] and coworkers have recently reported a palladium-catalyzed arylation reaction of olefinic compounds with aryl iodides and potassium acetate in methanol at 120°. We have independently discovered this reaction and find that it can be carried out under much more convenient laboratory conditions than were used by Mizoroki and that the reaction provides an extremely convenient method for preparing a variety of olefinic compounds.

The reaction is undoubtedly closely related to the known olefinic arylations and alkylations achieved at room temperature or below with palladium salts[2,3] using organomercury, -tin, or -lead compounds rather than organic halides. While the known reactions are very useful, they suffer from two major difficulties. There is often a problem of obtaining the necessary organomercury, -lead, or -tin compounds and there is the problem of working with thick slurries of salts, particularly if the reaction is carried out catalytically in palladium. This new method eliminates both difficulties.

Results and Discussion

It is well known that $Pd[P(C_6H_5)_3]_4$ reacts readily with a variety of organic halides to form oxidative addition products of the type $[P(C_6H_5)_3]_2Pd(X)R$.[4,5] In the reaction reported herein, a similar oxidative addition apparently occurs between palladium metal (formed by an *in situ* reduction of the palladium acetate initially

(1) T. Mizoroki, K. Mori, and A. Ozaki, *Bull. Chem. Soc. Jap.*, **44**, 581 (1971).

(2) R. F. Heck, *J. Amer. Chem. Soc.*, **90**, 5518 (1968).

(3) R. F. Heck, *ibid.*, **91**, 6707 (1969).

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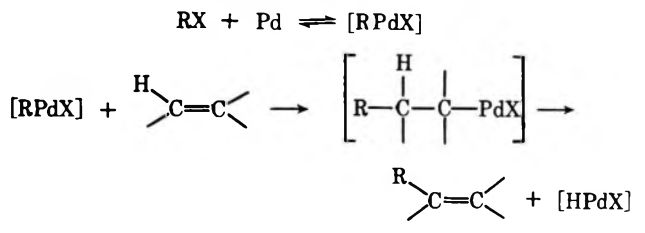
TABLE I

OLEFIN SUBSTITUTION REACTIONS WITH ORGANIC HALIDES[a]

Organic halide	Registry no.	Olefinic compd	Registry no.	Reaction time at 100°, hr	Product (yield, %)[b]	Registry no.	Mp of product, °C (reported)
Iodobenzene	591-50-4	Styrene	100-42-5	2	*trans*-Stilbene (75)	103-30-0	123–124 (124)[c]
Iodobenzene		4-Nitrostyrene	100-13-0	2	*trans*-4-Nitrostilbene (85)	736-31-2	153–155 (155–156)[d]
Iodobenzene		*cis*-1-Phenyl-1-propene	766-90-4	2	*cis*-1,2-Diphenyl-1-propene (7)	1017-22-7	*e*
					trans-1,2-Diphenyl-1-propene (12)	833-81-8	*e*
					1,2-Diphenyl-2-propene (4)		*e*
Iodobenzene		*trans*-1-Phenyl-1-propene	873-66-5	2	*cis*-1,2-Diphenyl-1-propene (21)		*e*
					trans-1,2-Diphenyl-1-propene (26)		*e*
Iodobenzene[f]		Methyl acrylate	96-33-3	1	*trans*-Methyl cinnamate (81)	1754-62-7	*e*
4-Iodoanisole	696-62-8	Methyl acrylate		5	*trans*-Methyl-*p*-methoxycinnamate (68)	3901-07-3	89–90 (90)[g]
Methyl 4-iodobenzoate	619-44-3	Styrene		2	*trans*-4-Carbomethoxystilbene (74)	34541-73-6	158–160 (158–159)[h]
1,4-Diiodobenzene	624-38-4	Styrene		15	*trans,trans*-*p*-Distyrylbenzene (67)	1608-41-9	266–267 (265)[i]
1,2-Diiodobenzene	615-42-9	Styrene		72	*trans,trans*-*o*-Distyrylbenzene (37)	27164-48-3	117–118 (117–119)[j]
Benzyl chloride	100-44-7	Methyl acrylate		15	*trans*-Methyl-4-phenyl-3-butenoate (67)	34541-74-7	*e*
					trans-Methyl-4-phenyl-2-butenoate (9)	34541-75-8	*e*
trans-β-Bromostyrene[l]	588-72-7	Methyl acrylate		72	*trans,trans*-Methyl-5-phenyl-2,4-pentadienoate (47)	24196-29-2	70–71 (71)[k]

[a] Except as noted, all reactions were carried out with 20 mmol of halide, 25 mmol of olefin, 20 mmol of tri-*n*-butylamine, and 0.2 mmol of palladium acetate with magnetic stirring in a steam bath with a water cooler condenser for the time indicated. [b] Yields were based upon the halide used and were of isolated, recrystallized products except where noted. [c] C. Hell, *Ber.*, 37, 453 (1904). [d] C. Weygand and R. Gabler, *ibid.*, 71, 2474 (1938). [e] Yields determined by gas chromatography. Products were not isolated. [f] Reaction mixture consisted of 10 mmol of iodobenzene, 20 mmol of methyl acrylate, 10 mmol of tri-*n*-propylamine, 0.1 mmol of palladium acetate, and 9 ml of 1-methyl-2-pyrrolidinone. [g] I. Heilbron, "Dictionary of Organic Compounds," Vol. 4, Oxford University Press, New York, N. Y., 1965. [h] R. C. Fuson and H. G. Cooke, Jr., *J. Amer. Chem. Soc.*, 62, 1180 (1940). [i] J. Dale, *Acta Chem. Scand.*, 11, 972 (1957). [j] D. H. Wadsworth, O. E. Schupp, III, E. J. Seus, and J. A. Ford, Jr., *J. Org. Chem.*, 30, 680 (1965). [k] G. Kresze, J. Firl, and H. Braun, *Tetrahedron*, 25, 4481 (1969). [l] The use of *cis*-β-bromostyrene also gave *trans,trans*-methyl-5-phenyl-2,4-pentadienoate, but only in 27% yield.

added by olefin) and certain organic halides, presumably producing very reactive solvated organopalladium(II) halides. These are probably the same compounds produced previously in the exchange reaction between palladium halides and organomercury compounds.[1,2] When prepared in the presence of olefinic compounds these organopalladium halides undergo an addition reaction with the olefin, and then the adduct decomposes by eliminating a hydridopalladium halide, forming the substituted olefinic compound.



The hydridopalladium halide product finally decomposes into hydrogen halide and palladium, which is then available to go through another reaction cycle. The accumulation of hydrogen halide in the reaction mixture has a very detrimental effect and must be neutralized by inclusion of a base. Mizoroki used potassium acetate, but we find a hindered amine to be better; tri-*n*-butylamine was generally used. Mizoroki carried out the reaction in methanol solution at 120°, which required pressurized reaction vessels. We find that the reaction can be carried out easily at steam bath temperatures in an open flask with a condenser, without use of a solvent. The reaction proceeds well in solvents such as 1-methyl-2-pyrrolidinone at 100° and atmospheric pressure also, but there seems to be no advantage to using them. The reactions we have carried out are listed in Table I.

Three types of halides were found to undergo the reaction: aryl, benzyl, and styryl. In the aryl examples, only the iodides reacted rapidly. Some product formed with bromobenzene, but the reaction was very slow even at 150°. Benzyl chloride and β-bromostyrene were less reactive than the aryl iodides but did give reasonable yields with longer reaction times. As with the reactions employing organomercury compounds,[1,2] these reactions tolerate a variety of functional groups such as nitro, methoxyl, and carbomethoxyl. Relatively low yields are obtained with olefinic compounds having methylene groups adjacent to the double bond. The low yields are apparently the result of the olefinic materials present forming inert, π-allylpalladium iodide derivatives with the catalyst, since, contrary to reactions with other types

of olefins, the palladium metal formed initially dissolves, and addition of more palladium acetate increases the yields of olefin substitution products substantially.

We have arbitrarily used 1 mol % palladium acetate as catalyst relative to the halide. Smaller amounts, no doubt, would be effective with the more reactive halides. Palladium metal deposited on charcoal may also be used as the catalyst but the reactions are slower and yields lower than with the finely divided metal obtained from *in situ* palladium acetate reduction.

This new vinylic substitution reaction is clearly an improvement over the mercurial reaction in many instances, particularly for preparing larger quantities of material. It does have some limitations, however, which the mercurial method does not have. The loss of stereochemistry in the phenylation of *cis*- and *trans*-1-phenyl-1-propene is one limitation. The isomerization appears to occur internally, probably through hydridopalladium halide–olefin π complexes, since neither starting olefin is isomerized to a detectable extent under the reaction conditions. In general, at the higher temperatures of the halide reactions, double bond migrations would be expected to be more serious. The benzyl chloride reaction showed this effect in producing a rearranged olefinic compound as the major product with methyl acrylate. The corresponding reaction

$$C_6H_5CH_2Cl + CH_2{=}CHCOOCH_3 + n\text{-}Bu_3N \xrightarrow{Pd} C_6H_5CH{=}CHCH_2COOCH_3 + C_6H_5CH_2CH{=}CHCOOCH_3 + n\text{-}Bu_3NH^+Cl^-$$

with benzylmercuric acetate and palladium acetate at room temperature gave only the expected *trans*-methyl-4-phenyl-2-butenoate.[6]

Other limitations include not being able to use base-sensitive compounds such as acrolein in the reaction and not being able to methylate by the halide reaction. Surprisingly, methyl iodide and methyl iodoacetate do not react with styrene under the usual conditions.

In spite of some limitations, the organic halide–olefinic substitution reaction should prove to be a useful synthetic reaction.

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Experimental Section

Materials.—All reagents were commercially available and used without further purification.

Gas Chromatography.—Samples were analyzed on a 6-ft silicon rubber on firebrick column at 175°. Known samples of the products were available from previous work.[1,2]

General Procedure for Vinylic Substitution with Organic Halides.—In a 25-ml round-bottomed flask containing a magnetic stirring bar was placed 0.2 mmol of anhydrous palladium acetate, 20 mmol of the organic halide, 20 mmol of tri-*n*-butylamine, and 25 mmol of the olefinic compound. A water-cooled condenser was placed on the flask and the mixture was stirred magnetically on a steam bath for the required length of time. On cooling the reaction mixtures often solidify. Several different product isolation procedures can be used. If the product is a high-melting solid, addition of water to the reaction mixture generally will give the product as a solid which can be separated and recrystallized with hot filtration to remove palladium metal present. Alternatively, if the reaction product is soluble in hot hexane, it may be extracted from the reaction mixture with boiling hexane several times. The extracts are then concentrated and either distilled or cooled to crystallize the product if it is a solid. A more general isolation procedure is to dilute the reaction mixture with cold dilute hydrochloric acid, extract the product with ether in the usual way, and distil the extracts. Two examples of the reaction are given in detail below.

trans-**4-Carbomethoxystilbene.**—A mixture of 0.045 g (0.2 mmol) of palladium acetate, 5.24 g (20 mmol) of methyl *p*-iodobenzoate, 2.86 ml (25 mmol) of styrene, and 4.74 ml (20 mmol) of tri-*n*-butylamine was stirred with a magnetic stirring bar in a steam bath under a water-cooled condenser for 2 hr. After cooling the reaction mixture was broken up with a spatula and stirred with about 100 ml of water in a beaker. After the lumps were thoroughly mashed, the insoluble product was separated by filtration. Recrystallization from 225 ml of boiling absolute ethanol with hot filtration through Celite gave 3.50 g (74%) of shiny plates, mp 158–160°.

trans,trans-*p*-**Distyrylbenzene.**—A mixture of 0.045 g (0.2 mmol) of palladium acetate, 3.30 g (10 mmol) of *p*-diiodobenzene, 2.86 ml (25 mmol) of styrene and 4.74 ml (20 mmol) of tri-*n*-butylamine was stirred magnetically in a steam bath under a water-cooled condenser for 15 hr. The mixture solidified during the heating. The solid reaction mixture was broken up with a spatula and stirred with water. The solid was filtered, washed several times with fresh water, and recrystallized from about 50 ml of hot dimethylformamide by filtering through Celite hot and adding water until crystals began to appear in the hot filtrate. After cooling, the pale yellowish product was isolated by filtration. After air drying, there was obtained 1.90 g (67%) of pale yellow crystals, mp 266–267°.

Registry No.—Palladium, 7440-05-3.

Preparation and Spectral Properties of β-Silyl-Substituted α,β-Unsaturated Ketones

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The preparation of 4,4-dimethyl-4-silacyclohexadien-1-one, 4,4-diphenyl-4-silacyclohexadien-1-one, 4,4-dimethyl-4-silacyclohex-2-enone, and 4-trimethylsilyl-3-buten-2-one is reported. The effect of the silyl center on the n → π* transition in their uv spectra is discussed.

Brook's discovery of the unusual spectral properties of α-silyl ketones stimulated research to determine the mechanism of silicon's effect.[2,3] A shift to lower energy in an n → π* transition can be produced either by lowering the energy of the excited π* state or by raising the energy of the ground state. Theoretical molecular orbital models indicate that the π* state could be stabilized by interaction with the empty d orbitals on silicon.[4,5] The energy level of the ground state n electrons has been probed by basicity[6] and appearance potential measurements.[7,8] The energy of the π* state has been determined from the polarographic half-wave potential for adding an electron to the system.[7,8]

A related effort has been the preparation of new systems in which different types of interaction of the silyl center with unsaturated chromophores may be discovered.[9-12]

Numerous α,β-unsaturated carbonyl systems have been prepared and their uv spectra reported. However, no system containing a silyl center interacting with a carbonyl functionality through a conjugating carbon–carbon double bond has been reported.[13]

We felt that such a system would be of interest for the following reasons. Stabilization of the n → π* transition in a α-silyl ketones is mainly produced by destabilization of the ground state by inductive electron release from the silyl center.[3,14] Stabilization of the excited π* state by overlap with the empty d orbitals on silicon also occurs but is much less important. In a β-silyl-substituted α,β-unsaturated ketone, inductive effects by silicon on the n electrons of oxygen will be much less important, since inductive effects are known to diminish rapidly with distance. Zimmerman has also calculated that in the n → π* state of an α,β-unsaturated ketone a charge separation develops in which the β carbon becomes partially negatively charged, while the carbonyl oxygen becomes partially positively charged.[15] Silicon is well known to stabilize a negative charge adjacent to it, possibly by

$$C{=}C{-}C{=}O \xrightarrow{h\nu} {}^{-\delta}C{-}C{=}C{-}O^{+\delta}$$

$d_\pi - p_\pi$ overlap.[16-18] Hence, we expected a β-silyl center to have a pronounced effect on the n → π* transition in an α,β-unsaturated ketone, owing to its ability to stabilize the polar excited π* state. To test these ideas, we have prepared 4,4-dimethyl-4-silacyclohexadien-1-one, 4,4-diphenyl-4-silacyclohexadien-1-one, 4,4-dimethyl-4-silacyclohex-2-enone, and 4-trimethylsilyl-3-buten-2-one.

We have previously reported the preparation of 4,4-dimethyl-4-silacyclohexadien-1-one[13] by the selenium dioxide oxidation of 4,4-dimethyl-4-silacyclohexanone.[19] While this method works, problems with removal of traces of foul-smelling organo selenium by-products caused us to seek a cleaner reaction. 4,4-Dimethyl-4-silacyclohexadien-1-one has also been prepared by oxidation of 4,4-dimethyl-4-silacyclohexanone using 2,3-dichloro-5,6-dicyanoquinone (DDQ) in refluxing benzene.[20,21]

4,4-Diphenyl-4-silacyclohexadien-1-one was prepared by oxidation of 4,4-diphenyl-4-silacyclohexanone, a previously unknown compound. Our sequence began with the preparation of diphenyldiallylsilane[22,23] by the *in situ* trapping of allyl Grignard by diphenyldichlorosilane. Diphenyldiallylsilane was converted to 4,4-diphenyl-4-sila-1,7-heptanediol by Brown's hydroboration–oxidation sequence[24,25] in high yield owing to the directive effect of the γ-silyl center.[26] The diol was oxidized using Jones reagent.[27,28] However, the yield was not good owing to competitive cleavage of the phenyl–silicon bonds by acid.[29,30] The diacid was

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esterified with methanol and cyclized by a modified Dieckmann reaction to close the six-membered ring.[31] The enolate anion formed in the cyclization was trapped by addition of trimethylchlorosilane to yield the corresponding silyl enol ether. This prevents the reverse reaction which occurs if quenching of the anion is slow as it is by addition of water.[32] This silyl enol ether was refluxed overnight in aqueous methanolic HCl. Hydrolysis of the trimethylsilyl group, decarboxylation of the β-keto acid, and a significant amount of undesired cleavage of phenyl–silicon bonds occurred in this step.[29,30] 4,4-Diphenyl-4-silacyclohexanone thus prepared was oxidized to the corresponding dienone by DDQ.[20,21]

4,4-Dimethyl-4-silacyclohex-2-enone could not be prepared by treatment of 4,4-dimethyl-4-silacyclohexanone[19] with either a limited amount of selenium dioxide or DDQ. When less than 1 equiv of oxidizing reagent was used, the only products obtained were the dienone and starting ketone. Apparently, the desired enone is more easily oxidized than the starting ketone.

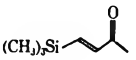
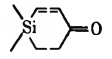
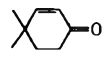
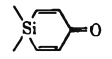
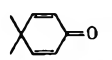
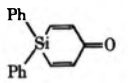
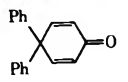
This problem was overcome as follows. 4,4-Dimethyl-4-silacyclohexanone was converted to the corresponding enol acetate by House's procedure.[33] The enol acetate was brominated with *N*-bromosuccinimide,[34] to form two allylic bromides in comparable yield. Apparently, the silyl center did not significantly stabilize a radical center either on a carbon α or on one β to it. The allylic bromide with the bromine β to silicon undergoes fragmentation during the subsequent solvolysis.[35,36] The allylic bromide with bromine α to silicon undergoes elimination to yield the desired enone (eq 1). Unfortunately, any intermediate enol acetate which was not brominated hydrolyzes to the starting ketone. Separation of the starting ketone from the product enone was accomplished by preparative gas chromatography.

4-Trimethylsilyl-3-buten-2-one was prepared from 4-trimethylsilylbutan-2-one[37] by the same reaction sequence used to prepare 4,4-dimethyl-4-silacyclohex-2-enone. Reaction with acetic anhydride leads to three isomeric enol acetates: 2-acetoxy-4-trimethylsilyl-*trans*-2-butene (I), 2-acetoxy-4-trimethylsilyl-*cis*-2-butene (II), and 2-acetoxy-4-trimethylsilyl-1-butene (III).[33] Only I and II react with *N*-bromosuccinimide to yield bromides capable of undergoing elimination to the desired product.[34]

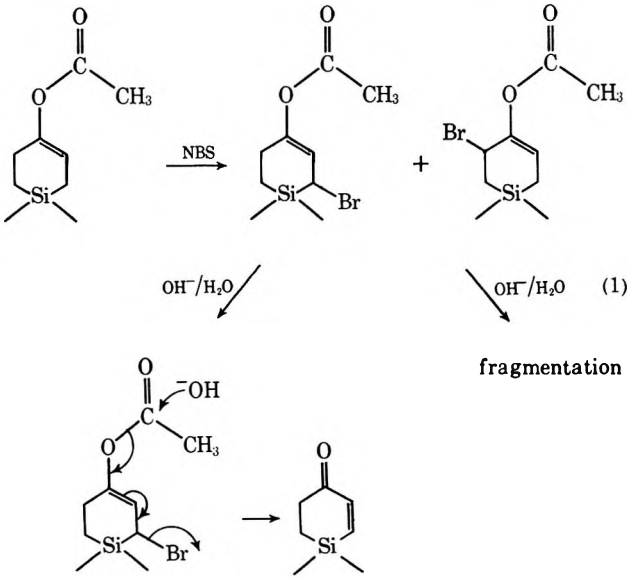
The ir of these silyl-substituted α,β-unsaturated ketones is of some interest. The C–O double-bond stretch in the silyl compounds is only slightly different from that observed in the analogous all-carbon compounds (see Table I). The only case where a significant difference is observed is 4,4-dimethyl-4-silacyclohexadien-1-one, which comes at 1648 cm^{-1} compared to 1664 cm^{-1} for 4,4-dimethylcyclohexadien-1-one.[15] By comparison, the C–O stretch of trimethylsilyl methyl ketone comes at 1645 cm^{-1},[38] while that of *tert*-butyl methyl ketone, the carbon analog, comes at 1718 cm^{-1}.[39] Another example is trimethylsilyl phenyl ketone, whose C–O double-bond stretch comes at 1618 cm^{-1},[40] compared with 1680 cm^{-1} for *tert*-butyl phenyl ketone.[41] Clearly, the ground-state C–O double bond is much more perturbed in α-silyl ketones than in our silyl-substituted α,β-unsaturated ketones.

On the other hand, the C–C double-bond stretch in our silyl compounds all comes at considerably longer wavelength than in the analogous all-carbon compounds. However, the C–C double bond of trimethylvinylsilane is also shifted[42] to 1597 cm^{-1}, whereas the

TABLE I
INFRARED SPECTRAL COMPARISONS[a]

Compd	C=O stretch, cm^{-1}	C=C stretch, cm^{-1}
Trimethylvinylsilane		1597[b]
	1683 (s) 1701 (w)	1586 (w)
	1685 (s) 1706 (w)	1620
	1678 (s)	1573 (w)
	1684 (s)	1626 (w)
	1648 (s)	1584 (s)
	1664 (s)	1630 (s)
	1653 (s)	1586
	1652 (s)	1626[c]

[a] All spectra were determined on a Beckman IR-7 instrument in cyclohexane solution. [b] Reference 39. [c] Reference 46.



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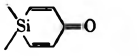
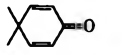
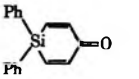
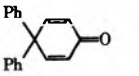
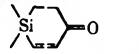
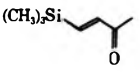
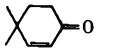
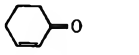
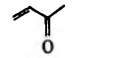
C–C double bond of normal 1-alkenes comes at ~1650 cm^{-1}.[43] Hence, we believe the ir spectra indicate little perturbation of the ground state of the α,β-unsaturated carbonyl chromophore in our compounds.

In the uv spectra of these β-silyl-substituted α,β-unsaturated ketones, the n → π* transitions were identified by their characteristic vibrational fine structure as well as by the fact that the band shifted to shorter wavelengths in ethanol than in cyclohexane[44] (see Experimental Section for details). Authentic samples of 4,4-dimethylcyclohex-2-enone,[45] 4,4-dimethylcyclohexadien-1-one,[15] 4,4-diphenylcyclohexadien-1-one,[46] 2-cyclohexenone, and methyl vinyl ketone were prepared and their spectral properties compared under identical conditions.

The λ_{max} of the n → π* transition in all of the silyl compounds is shifted to longer wavelength than their carbon analogs. The transition for 4,4-dimethyl-4-silacyclohexadien-1-one is stabilized by 5.6 kcal/mol compared with that of 4,4-dimethylcyclohexadien-1-one (see Table II). This transition is stabilized by 5.2 kcal/mol in 4,4-diphenyl-4-silacyclohexadien-1-one compared with 4,4-diphenylcyclohexadien-1-one.[46] Comparison of energies of the 0–0 bands[15] of the n → π* transitions for these compounds yields similar values for the stabilization by the silyl center. This observation that a diphenylsilyl group has approximately the same effect as a dimethylsilyl group supports our view that the effect of the silyl center on the n → π* transition is mainly due to stabilization of the polar π* excited state. This is true, since a diphenylsilyl group is expected to have a smaller inductive electron-releasing effect than a dimethylsilyl group. Phenyl groups are well known to be inductively electron withdrawing.[47]

Table II

Ultraviolet Spectral Data n → π* Transitions in Cyclohexane

Compd	Registry no.	λ_{max} in Å (band) (ε)	0–0 band in Å
	30518-19-5	3725 (0–3) (16)	4180
	1073-14-9	3470 (0–3) (15)	3885[a]
	34564-64-2	3740 (0–3) (19)	4205
	13304-12-6	3500 (0–3) (25)	3920[b]
	34564-66-4	3500 (0–2) (35)	3865
	34564-67-5	3380 (0–3) (49)	3860
	1073-13-8	3400 (0–2) (26)	
	930-68-7	3430 (0–2) (28)	
	78-94-4	3300 (0–3) (22)	

[a] The 0–0 band for 4,4-dimethylcyclohexadien-1-one has been reported at 3770 Å (see ref 15). We have prepared this compound from 4,4-dimethylcyclohex-2-enone[45] by oxidation with either selenium dioxide or DDQ. In both cases we find the 0–0 band at 3885 Å. However, this may not be an experimental discrepancy but a difference in interpretation. The experimental section of ref 15 reports a band at 3883 Å in cyclohexane. [b] Reference 15.

Further, stabilization by the silyl center in α,β-unsaturated ketones appears to be additive. Comparison of the λ_{max} for the n → π* transition in 4,4-dimethyl-4-silacyclohex-2-enone with that observed for 4,4-dimethylcyclohex-2-enone and 2-cyclohexenone indicates a stabilization by the silyl center of ~2.4 kcal/mol. Comparison of the λ_{max} for the n → π* transition in 4-trimethylsilyl-3-buten-2-one with that observed in methyl vinyl ketone indicates a stabilization by the silyl center of ~2.1 kcal/mol. Thus, the stabilization by a β-silyl center of the n → π* transition in an enone system is approximately half that observed in the β-silyl dienone systems. Apparently, the geometry about the carbon–carbon double bond is not important, since the open-chain silyl enone in which the carbon–carbon double bond is trans shows almost the same stabilization.

In conclusion, the effect of a β-silyl center on the n → π* transition in α,β-unsaturated ketones is much smaller than the stabilization by silicon in α-silyl ketones. The mechanism of this stabilization may be primarily the interaction of the silyl center with the polar excited π* state.

This difference in inductive effects has been observed in the spectra of α-silyl ketones. The λ_{max} of the n → π* transition in *tert*-butyl methyl ketone comes at 34,800 cm^{-1}, whereas in trimethylsilyl methyl ketone it comes at 26,900 cm^{-1}.[14] Thus, the stabilization of the n → π* transition by a trimethylsilyl group amounts to 22.6 kcal/mol. On the other hand, the λ_{max} of the n → π* transition in triphenylmethyl methyl ketone comes at 33,100 cm^{-1}, whereas in triphenylsilyl methyl ketone it comes at 26,600 cm^{-1}.[14] Thus, the stabilization of the n → π* transition by a triphenylsilyl group amounts to 18.5 kcal/mol. In the corresponding phenyl ketones, a trimethylsilyl group is found to stabilize the n → π* transition by ~4 kcal/mol more than a triphenylsilyl group when both are compared with those of the corresponding carbon compounds. This difference in stabilization probably occurs because the trimethylsilyl group has a larger inductive electron-releasing effect, causing a greater destabilization of the ground state.

Experimental Section

All reactions were carried out under an atmosphere of nitrogen. Melting points are uncorrected. Ir spectra were determined in CCl_4 solution on a Perkin-Elmer 337, unless otherwise noted. Nmr spectra were run on a Varian HA-100 using 10% solutions in CCl_4. Benzene, methylene chloride, 1,2-dichloroethane, or tetramethylsilane was used as an internal standard. Microanalysis was performed by Elek Microanalytical Laboratory or by Schwarzkopf Microanalytical Laboratory. All uv spectra were run on a Cary 14 in either spectro-quality cyclohexane or in ethanol. High resolution mass spectra were run on an AEI MS-902 instrument. Exact mass determination of the composi-

(43) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Methuen, London, 1958, p 35.

(44) N. J. Turro, "Molecular Photochemistry," W. A. Benjamin, New York, N. Y., 1967, p 46.

(45) W. G. Dauben, G. W. Schaffer, and N. D. Vietmeyer, *J. Org. Chem.*, **33**, 4060 (1968).

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(47) B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **71**, 1159, 1171 (1952).

tion of important ions were carried out at a resolution of at least 10,000 by peak matching with peaks of known mass of perfluorokerosene: ionizing voltage 70 eV; filament emission 480 μA; source temperature 150°.

4,4-Dimethyl-4-silacyclohexadien-1-one.—In a dry 50-ml round-bottom flask equipped with a reflux condenser and a magnetic stirring bar 1 g (7 m*M*) of 4,4-dimethyl-4-silacyclohexanone,[19] 5.0 g (22 m*M*) of DDQ, and 30 ml of dry benzene were refluxed for 24 hr.[20,21] It was then chromatographed through a short alumina column with ether. The solvent was removed by evaporation under reduced pressure at 25°. The residue was then bulb to bulb distilled at 0.1 mm. Essentially pure 4,4-dimethyl-4-silacyclohexadien-1-one (600 mg) was thus obtained. Analytical samples were purified by preparative gas chromatography on a 0.25 in. × 5 m 20% DC QF-1 column at 130°. (For ir data, see Table I). The uv spectrum showed peaks at 4180 Å (ε 4), 3985 (9), 3885 (13), 3725 (16), 3570 (14), 3440 (10), 3220 (6), and 2275 (1.8×10^4) in cyclohexane. In 95% ethanol one observes peaks at 3540 Å (ε 30) and 2330 (1.2×10^4). The nmr spectrum contained the following: s (6 H) at δ 0.22, d (2 H) at 6.71 (J = 15 Hz), d (2 H) at 6.98 ppm (J = 15 Hz) in CH_2Cl_2; s (6 H) δ 0.26, d (2 H) at 6.70, d (2 H) at 6.93 ppm (J = 15 Hz) in CCl_4; s (6 H) at δ 0.22, d (2 H) at 6.71, d (2 H) at 7.12 ppm (J = 15 Hz) in acetone. This type of shift of the β proton in α,β-unsaturated ketones has been observed previously.[48] The β proton shifts downfield in solvents of higher dielectric constant. *Anal.* Calcd for $C_7H_{10}OSi$: C, 60.82; H, 7.29. Found: C, 60.55; H, 7.24.

Diphenyldiallylsilane prepared from allylmagnesium bromide and diphenyldichlorosilane in THF had physical properties in agreement with literature values.[22,23] The ir spectrum had a C–C double-bond stretch at 1630 cm^{-1}; nmr d (4 H) at δ 2.05 (J = 9.5 Hz), m (4 H) at 4.85, m (2 H) at 5.75, m (10 H) at 7.32 ppm.

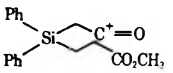
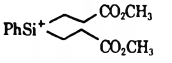
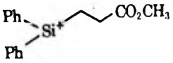
4,4-Diphenyl-4-sila-1,7-heptanediol was prepared by hydroboration and oxidation of diphenyldiallylsilane.[24,25] The crude product (87% yield) was purified by recrystallization from ether–*n*-hexane, mp 83–85°. Its ir spectrum had a broad O–H band centered at 3330 cm^{-1}; nmr (in acetone-d_6) m (4 H) at δ 1.14, m (4 H) at 1.58, m (4 H) at 3.52, s (2 H) at 3.77, m (10 H) at 7.35 ppm. *Anal.* Calcd for $C_{18}H_{24}O_2Si$: C, 71.95; H, 8.05. Found: C, 71.80; H, 7.94.

4,4-Diphenyl-4-sila-1,7-heptanedioic Acid.—In a 5-l. flask equipped with a mechanical stirrer, a thermometer, and an addition funnel 170 g (0.57 mol) of 4,4-diphenyl-4-sila-1,7-heptanediol was dissolved in 700 ml of reagent acetone in an ice–salt bath; 1.14 l. of Jones reagent was added at a rate such that the temperature remained below 20°.[25,26] The mixture was stirred for an additional 15 min. The organic layer was separated, and the aqueous layer was extracted with three 500-ml portions of ether. The combined organic layers were extracted with 20% sodium hydroxide solution until the extract was basic. This basic aqueous solution was then acidified with concentrated HCl and extracted with three 500-ml portions of ether. The ether extracts were dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed by evaporation under reduced pressure. A 50% yield of crude diacid was obtained. The diacid was purified by recrystallization from acetone–*n*-hexane, mp 143–144°. Its ir spectrum in CH_3CN solvent had a C–O double-bond stretch at 1740 cm^{-1}; nmr (acetone-d_6) m (4 H) at δ 1.47, m (4 H) at 2.33, m (10 H) at 7.47, s (2 H) at 10.40 ppm. *Anal.* Calcd for $C_{18}H_{20}O_4Si$: C, 65.82; H, 6.14%. Found: C, 65.98; H, 6.13.

Dimethyl-4,4-diphenyl-4-sila-1,7-heptanedioate.—Crude diacid (90 g) dissolved in 600 ml of methanol containing 5 ml of concentrated H_2SO_4 in a 1-liter flask was refluxed overnight. The volume of the solution was reduced to one-third by evaporation under reduced pressure. Ether (500 ml) was added and the solution was extracted twice with 100-ml portions of water followed by 100-ml portions of 10% NaOH until the extracts were basic. The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed by evaporation under reduced pressure. The residue was distilled through a short-path distillation column, bp 150° (0.001 mm).

An 80% yield of a light yellow oil was obtained. Its ir spectrum in CCl_4 solution had a strong C–O double-bond stretch at 1745 cm^{-1}; nmr m (4 H) at δ 1.39, m (4 H) at 2.25, s (6 H) at 3.47, m (10 H) at 7.36 ppm. Its mass spectrum (Table III) was characterized by an acylium ion and by two siliconium ions formed by fragmentation at the quaternary silyl center. The exact masses of the two intense siliconium ions were determined.

TABLE III

	Mass	Rel intensity, %
	325	11
	279[a]	100
	269[b]	93

[a] Calcd for $C_{14}H_{19}O_4Si$: 279.1052. Found: 279.1040. [b] Calcd for $C_{16}H_{17}O_2Si$: 269.0997. Found: 269.0954.

4,4-Diphenyl-4-silacyclohexanone.—In a dry 2-l. three-necked round-bottom flask equipped with a mechanical stirrer, a pressure equalizing addition funnel, and a reflux condenser was placed 1 mol of sodium hydride and 1 l. of dry toluene. The mixture was stirred at reflux, while 70 g (0.22 mol) of dimethyl 4,4-diphenyl-4-sila-1,7-heptanedioate was added during 4 hr, followed by 66 g (0.6 mol) of trimethylchlorosilane.[31] The mixture was filtered and stripped of solvents at atmospheric pressure. The residue was refluxed overnight with 300 ml of methanol, 100 ml of H_2O, and 25 ml of concentrated HCl. The solution was extracted with three 100 ml portions of ether. The combined organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed by evaporation under reduced pressure. The residue was distilled through a 10-cm Vigreux column. A central fraction, bp 190° (0.5 mm), 10 g (12% yield), solidified on standing and was further purified by recrystallization from ether–*n*-hexane, mp 93–94°. Its ir spectrum was characterized by a C–O double-bond stretch at 1720 cm^{-1} in CCl_4 solution; nmr (1,2-dichloroethane) m (4 H) at δ 1.46, m (4 H) at 2.54, m (10 H) at 7.43 ppm. *Anal.* Calcd for $C_{17}H_{18}OSi$: C, 76.64; H, 6.81. Found: C, 76.58, 76.82; H, 6.82, 6.77.

4,4-Diphenyl-4-silacyclohexadien-1-one.—In a dry 100-ml round-bottom flask equipped with a reflux condenser and a magnetic stirring bar was placed 2 g (7.5 m*M*) of 4,4-diphenyl-4-silacyclohexanone, 5.1 g (22.6 m*M*) of 2,3-dichloro-5,6-dicyanoquinone (DDQ) and 50 ml of benzene. The mixture was refluxed for 24 hr with stirring.[20,21] It was then chromatographed through a short alumina column with ether. Solvent was removed by evaporation under reduced pressure; 800 mg of a thick yellow oil was obtained (40% yield). The oil solidified on standing at 0°. It was purified by recrystallization from methanol at 0°, to yield a slightly yellow solid: mp 67.3–67.9°; for ir spectrum, see Table I; nmr (CCl_4) d (2 H) at δ 6.89 (J = 14.8 Hz), d (2 H) at 7.16 (J = 14.8 Hz), m (10 H) at 7.40 ppm; nmr (acetone) δ d (2 H) at 6.96 (J = 14.8 Hz), m (12 H) at 7.50 ppm;[48] uv (cyclohexane) peaks at 4205 Å (ε 3), 4010 (9), 3900 (15), 3740 (19), 3590 (15), 3460 (9), and 3320 (3) in cyclohexane; uv (95% EtOH) λ_{max} 3540 Å (ε 28). *Anal.* Calcd for $C_{17}H_{14}OSi$: C, 77.82; H, 5.38. Found: C, 77.78; H, 5.62.

1-Acetoxy-4,4-dimethyl-4-sila-1-cyclohexene.—Acetic acid and acetic anhydride was slowly distilled through a 30-cm spiral wire distillation column from a stirred solution of 19.9 g (0.14 mol) of 4,4-dimethyl-4-silacyclohexanone[19] in 40 ml of acetic anhydride containing 300 mg of *p*-toluenesulfonic acid.[33] The amount of acetic acid in the distillate was determined by pmr integration. After 5 hr the theoretical amount of acetic acid had been collected. One gram of sodium acetate was then added to neutralize the *p*-toluenesulfonic acid. The solution was cooled, diluted with 150 ml of ether, and extracted with two 50-ml portions of sodium bicarbonate solution. It was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed by evaporation under reduced pressure at room temperature. The residue was distilled through a 10-cm Vigreux column. A central fraction, 15.5 g (60% yield), bp 116–117° (30 mm), was collected. Its ir spectrum was characterized by a C–O double-bond stretch at 1750 and a C–C double-bond stretch at 1680 cm^{-1} (weak) (this is typical for C–C double bonds in enol acetates[33]); nmr s (6 H) at δ 0.03, t (2 H) at 0.69 (J = 7 Hz), d of t (2 H) at 1.11 (J_d = 5.5 Hz, J_t = 2 Hz), s (3 H) at 1.92, t (2 H) at 2.19 (J = 7 Hz), t of t (1 H) at 5.24 ppm (J_t = 5.5 Hz, J_t = 1 Hz). *Anal.*

(48) F. H. Cottee and C. J. Timmons, *J. Chem. Soc. B*, 326 (1968).

Calcd for $C_9H_{16}O_2Si$: C, 58.65; H, 8.75. Found: C, 58.48; H, 8.80.

4,4-Dimethyl-4-silacyclohex-2-enone.—In a dry 500-ml flask equipped with a reflux condenser and a magnetic stirring bar was placed 15.5 g (84.4 m*M*) of 1-acetoxy-4,4-dimethyl-4-sila-1-cyclohexene, 16.5 g (92.6 m*M*) of *N*-bromosuccinimide, 100 ml of reagent carbon tetrachloride, and a catalytic amount of benzoyl peroxide. The mixture was heated to reflux.[34] Reaction was complete within 3 min. Succinimide was removed by filtration. CCl_4 was removed by evaporation under reduced pressure. To the residue was added 150 ml of THF and 25 g of Na_2CO_3 dissolved in 150 ml of water.[34] This solution was heated at reflux for 1 hr. The solution was cooled and the layers were separated. The aqueous layer was extracted with two 50-ml portions of ether. The combined organic layers were dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed by evaporation under reduced presure at 25°. The residue was chromatographed on an alumina column. A mixture of the desired enone and the starting ketone was eluted with 1:1 ether–*n*-hexane. The ketone and enone were separated by preparative gas chromatography on a 0.25 in. × 5 m 20% DC QF-1 column at 120°. For its ir spectrum, see Table 1. Its nmr spectrum (CCl_4) contained the following: s (6 H) at δ 0.19, m (2 H) at 1.03, m (2 H) at 2.56, d (1 H) at 6.47 (J = 14.5 Hz), d (1 H) at 6.82 ppm (J = 14.5 Hz). The chemical shifts of the downfield doublets showed a solvent dependence with the cis-β proton shifting downfield in solvents of higher dielectric constant.[48] In cyclohexane the doublets were found at 6.45 and 6.72 ppm; in dioxane at 6.50 and 6.88 ppm; in acetone at 6.48 and 6.97 ppm; and finally in acetonitrile at 6.51 and 7.01 ppm. The uv spectrum in cyclohexane showed peaks at 3865 Å (ε 7), 3675 (23), 3500 (35), 3390 (35), 3260 (26), 3120 (15) and 2155 (1.0×10^4). In 95% EtOH one observes peaks at 3295 Å (ε 30) and 2220 (3.7×10^3). *Anal.* Calcd for $C_7H_{12}OSi$: C, 59.94; H, 8.62%. Found: C, 59.79; H, 8.85.

2-Acetoxy-4-trimethylsilyl-2-butene.—In a dry 100-ml flask equipped with a reflux condenser and a magnetic stirring bar was placed 5.5 g (38.2 m*M*) of 4-trimethylsilyl-2-butanone,[37] 50 ml of acetic anhydride, and 300 mg of *p*-toluenesulfonic acid.[33] The mixture was stirred at reflux overnight. The reflux condenser was then replaced with a 10-cm Vigreux column, 40 ml of solvent was removed by distillation over 1 hr, and 1 g of sodium acetate was then added to neutralize the acid. After cooling, the mixture was placed in a separatory funnel with 150 ml of ether. The organic layer was washed with three 20-ml portions of sodium bicarbonate solution. It was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed by evaporation under reduced pressure. The residue was distilled through a 10-cm Vigreux column. A fraction, 2 g (30% yield), bp 100–120°/(30 mm), was collected. The three possible enol acetates were separated by preparative gas chromatography on a 0.25 in. × 5 m 20% FFAP column at 120°. The relative ratios of 2-acetoxy-4-trimethylsilyl-*trans*-2-butene (I), 2-acetoxy-4-trimethylsilyl-*cis*-2-butene (II), and 2-acetoxy-4-trimethylsilyl-1-butene (III) were found to be I:II:III 5:3:1. The ir spectrum of (III) showed a C–O double-bond at 1740 cm^{-1}. The ir spectra of pure I and II were characterized by a C–O double-bond stretch at 1755 cm^{-1}. The nmr spectrum of I showed s (9 H) at δ 0.0, d of quartets (2 H) at 1.30 (J_d = 8.2 Hz, J_q = 1.2 Hz), d of t (3 H) at 1.85 (J_d = 1.2 Hz, J_t = 1.2 Hz), s (3 H) at 1.98, and t of quartets (1 H) at 4.83 ppm (J_t = 8.2 Hz, J_q = 1.2 Hz). The nmr spectrum of II was nearly identical. The mass spectrum of I was determined. Major ions at P − 42 and P − 43 were observed. Loss of ketene (P − 42) to form the parent ketone is a known process in the mass spectra of enol acetates.[49,50] Loss of $CH_3C{=}O$ by α cleavage is often observed in the mass spectra of acetates. The exact mass of the parent ion and the P − 42 ion were determined. Parent ion·$^+$ calcd for $C_9H_{18}O_2Si$: 186.1075. Found: 186.1076. P − 42 calcd for $C_7H_{16}OSi$: 144.0970. Found: 144.0959. *Anal.* Calcd for $C_9H_{18}O_2Si$: C, 58.01; H, 9.74. Found: C, 57.74; H, 9.71.

4-Trimethylsilyl-3-buten-2-one.—In a dry 100-ml flask equipped with a reflux condenser and a magnetic stirring bar 2.0 g (10.8 m*M*) of 2-acetoxy-4-trimethylsilyl-2-butene was refluxed with 1.8 g (10.1 m*M*) of *N*-bromosuccinimide in 25 ml of CCl_4 and a catalytic amount of benzoyl peroxide.[31] The reaction was complete within 3 min. Succinimide was removed by filtration. CCl_4 was removed under reduced pressure at 25°. The residue in 20 ml of THF was stirred overnight at 25° with 5 g of Na_2CO_3 in 20 ml of water. The aqueous layer was separated and extracted twice with two 20-ml portions of ether. The combined organic layers were washed with a saturated NaCl solution, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure at room temperature. The residue was bulb to bulb distilled at 0.15 mm; 1.01 g of volatile material was obtained. The desired enone was separated from the starting ketone by preparative gas chromatography on a 0.25 in. × 5 m DC QF 1-column at 130°: for ir, see Table I; nmr (CCl_4) s (9 H) at δ 0.11, s (3 H) at 2.15, d (1 H) at 6.29 (J = 19.4 Hz), d (1 H) at 6.87 ppm (J = 19.4 Hz); uv (cyclohexane) peaks at 3860 Å (ε 7), 3660 (28), 3510 (44), 3380 (49), 3280 (42), 2200 (1.1×10^4); uv (95% EtOH) peaks at 3260 Å (ε 60.5), 2230 (1.3×10^4). The base peak in the mass spectrum of 4-trimethylsilylbut-3-en-2-one was a siliconium ion formed by loss of a methyl radical from the parent ion. The exact mass of the parent ion and the P − 15 were determined. Parent ion·$^+$ calcd for $C_7H_{13}OSi$: 142.0813. Found: 142.0784. P − 15 calcd for $C_6H_{11}OSi$: 127.0578. Found: 127.0550.

Registry No.—I, 34564-95-9; II, 34564-96-0; III, 34564-70-0; diphenyldiallylsilane, 10519-88-7; 4,4-diphenyl-4-sila-1,7-heptanediol, 34564-72-2; 4,4-diphenyl-4-sila-1,7-heptanedioic acid, 34564-73-3; dimethyl 4,4-diphenyl-4-sila-1,7-heptanedioate, 34564-74-4; 4,4-diphenyl-4-silacyclohexanone, 34564-75-5; 1-acetoxy-4,4-dimethyl-4-sila-1-cyclohexene, 34599-24-1.

Acknowledgments.—We would like to thank the Research Corporation, Caltech President's Fund NASA Contract NAS 7-100, and finally the National Institutes of Health for a Biomedical Sciences Support Grant FR-07012-04.

(49) D. G. B. Boocock and E. S. Waight, *J. Chem. Soc. B.*, 258 (1968).
(50) W. Freytag and H. Scharmann, *Chem. Ber.*, **100**, 3457 (1967).

The Reaction of Diphenylcyclopropenone with 1-Azirines. Synthetic and Mechanistic Implications[1]

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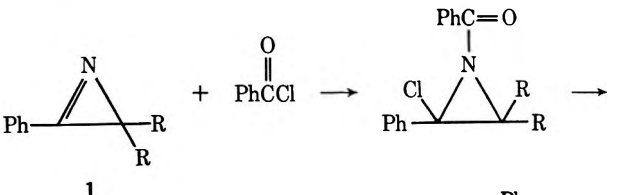
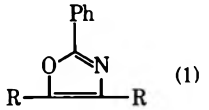
Received October 13, 1971

1-Azirines 1 react with diphenylcyclopropenone (2) to produce 1:1 adducts, which were proven to be 2,3-diphenyl-4-pyridones 6. That the 3 substituents in 6 originate from the 3 substituents on the azirine was shown by independent synthesis of 6a as well as by isolation of the 3*H*-4-pyridone 10 when 2-phenyl-3,3-dimethylazirine was used as a substrate. These results suggest a nucleophilic attack by the azirine nitrogen on C-2 of the cyclopropenone with subsequent rupture of the azirine 3–1 bond (C–N). The mechanistic pathway of the reaction is discussed.

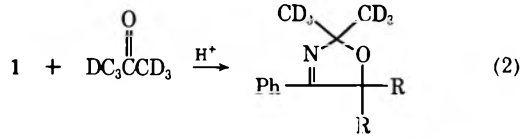
Both 1-azirines (1) and cyclopropenones (2) represent versatile substrates which can act either as dipoles or dipolarophiles as well as by way of ionic intermediates. For instance, examples have recently become known in which additions to azirines occur across the C=N bond (eq 1),[2] the C–N bond (eq 2),[3] or the C–C bond in these heterocycles (eq 3).[4]



1



(1)



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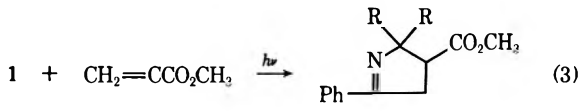


(3)

Similarly, ample evidence has accumulated for addition across the C=C bond (eq 4),[5] or the C=O bond of cyclopropenones (eq 5)[6] as well for regioselective ring opening of the C–C bond in these systems (eq 6,7).[7,8]

Our extensive studies of the chemical behavior[2,9] of azirines made it desirable to explore the interaction between this strained ring system and a polar cyclopropenone, with emphasis on reaction conditions, structure of products, and mechanistic implications.

(1) Chemistry of Small Ring Heterocycles. XIX. For the previous paper in this series, see ref 9e.

(2) F. W. Fowler and A. Hassner, *J. Amer. Chem. Soc.*, **90**, 2875 (1968).

(3) N. J. Leonard and B. Zwanenburg, *ibid.*, **89**, 4456 (1967).

(4) A. Padwa and J. Smolanoff, *ibid.*, **93**, 548 (1971).

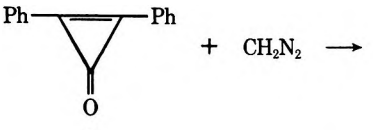
(5) P. T. Izzo and A. S. Kende, *Chem. Ind. (London)*, 839 (1964); R. Breslow, T. Eicher, A. Krebs, R. A. Peterson, and J. Posner, *J. Amer. Chem. Soc.*, **87**, 1320 (1965).

(6) L. Paquette, T. Barton, and N. Horton, *Tetrahedron Lett.*, **No. 50**, 5039 (1967).

(7) E. V. Dehmlow, *ibid.*, **51**, 5177 (1967).

(8) F. Toda, T. Mitote, and K. Akagi, *Chem. Commun.*, **5**, 228 (1969).

(9) (a) A. Hassner and F. W. Fowler, *J. Amer. Chem. Soc.*, **90**, 2869 (1968); (b) A. Hassner, R. J. Isbister, R. B. Greenwald, J. T. Klug, and E. C. Taylor, *Tetrahedron*, **25**, 1637 (1969); (c) A. Hassner and R. J. Isbister, *J. Amer. Chem. Soc.*, **91**, 6126 (1969); (d) A. Hassner, J. O. Currie, A. S. Steinfeld, and R. F. Atkinson, *Angew. Chem.*, **82**, 772 (1970); (e) D. J. Anderson and A. Hassner, *J. Amer. Chem. Soc.*, **93**, 4339 (1971).



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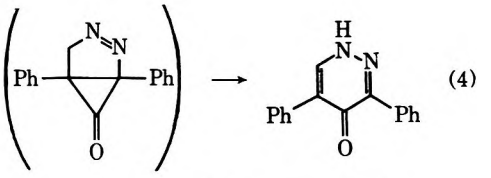

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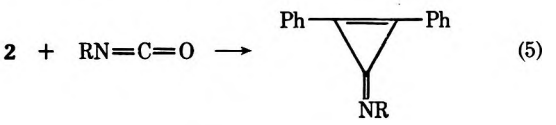
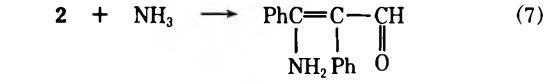


(5)

(6)



(7)

Results and Discussion

Diphenylcyclopropenone (2) underwent a slow reaction with mono- and disubstituted azirines (1) at temperatures above 100° (see Table I). Refluxing toluene

TABLE I

FORMATION OF PYRIDONE 6 BY HEATING OF AZIRINE 1 WITH CYCLOPROPENONE 2 IN TOLUENE

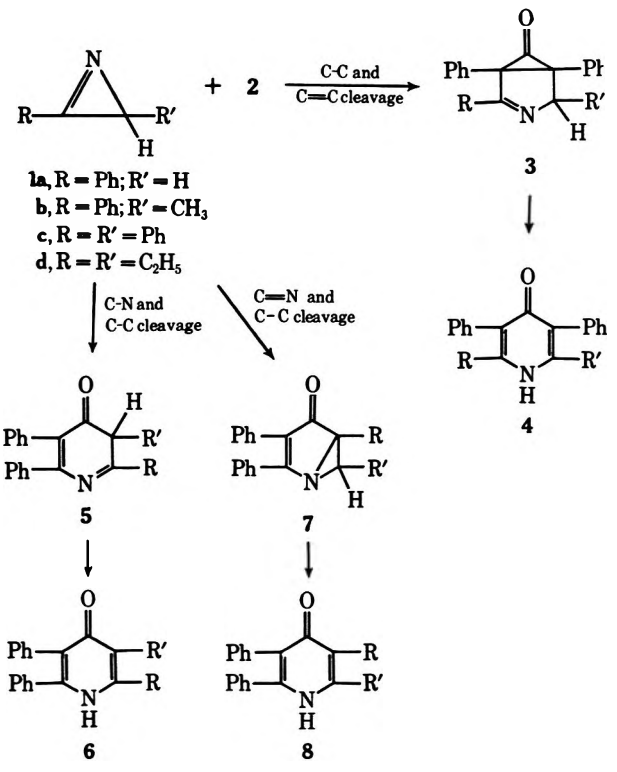
Azirine	Pyridone	Reaction time, days	Yield, %[a]
1a	2,3,6-Triphenyl-4(1*H*)-pyridone (6a)	2	27
1b	2,3,6-Triphenyl-5-methyl-4(1*H*)-pyridone (6b)	2 (4)	33 (50)
1c	2,3,5,6-Tetraphenyl-4(1*H*)-pyridone (6c)	2	27
1d	2,3-Diphenyl-5,6-diethyl-4(1*H*)-pyridone (6d)	3	33
9	3,3-Dimethyl-2,5,6-triphenyl-4(3*H*)-pyridone (10)	2	67[b]

[a] Yield actually represents per cent conversion, since examination of the alkyl region in the nmr spectra of the ether-soluble fractions showed only azirine for 1a–d, and azirine plus adduct for 9. The yields could be improved by refluxing for longer times, as shown with 1b. [b] By nmr; the isolated yield of pyridone 10 was 35% since it is appreciably soluble in ether.

was a convenient medium in which the rate of product formation was able to compete with polymerization of **2** and destruction of azirine **1**. Under these reaction conditions the crude product contained an appreciable amount of unreacted **1**. The product was isolated upon evaporation of the solvent and trituration with ether. The ether-insoluble material was a 1:1 adduct as indicated by elemental analysis, mass spectra, and nmr integration.

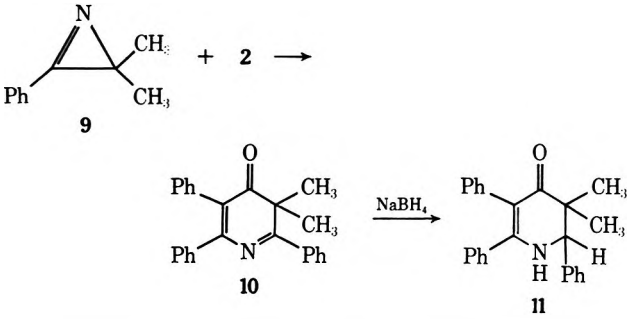
On the basis of the chemical behavior of **1** and **2** discussed above, a number of 2- and 4-pyridones, 3-hydroxypyridines, and azabicyclocyclohexanones come into consideration for the adduct. The ir spectra of adducts **6a** and **6b** (**6c** and **6d** were insoluble in $CHCl_3$) in dilute chloroform showed a sharp absorption ($W_{1/2}$ = 15 Hz) at 3400 cm^{-1}, a position and half-width reportedly[10a] characteristic of amidic NH. The only intense absorption in the carbonyl region of 1600–1800 cm^{-1} occurred at 1625 cm^{-1}. Such low carbonyl absorption is observed for 4-pyridones,[10b] suggesting **4**, **6**, and **8** as possible structures for the adducts. The pathways to these products involve C–C, C–N, or C=N cleavage of the azirine coupled with C=C or C–C cleavage of the cyclopropenone (see Scheme I).

SCHEME I



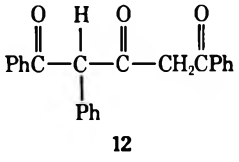
Structure **4** was eliminated, since the adduct of azirine **1d** with **2** showed two nonequivalent ethyl groups in the nmr spectrum.[11] Of the two remaining possibilities structure **8** is derived from a fused aziridine **7** prior to aromatization (Scheme I). If a 3,3-disubstituted azirine were used as a substrate, one might expect to isolate a bicyclic intermediate of type **7** because aromatization would require an energetically more unfavorable alkyl migration.

In fact, the adduct of 2-phenyl-3,3-dimethylazirine (**9**) showed two equivalent methyl groups in the nmr (not expected for a bicyclic aziridine of type **7** containing a geminal dimethyl grouping). Reduction of this adduct with $NaBH_4$ gave a material which showed two *non*equivalent methyl groups in the nmr spectrum. The ir spectrum showed a sharp NH peak at 3400 cm^{-1} and C=O absorption at 1625 cm^{-1}. In addition, the



uv spectrum, λ_{max} 230 nm (ϵ 15,000) and 345 (10,000), as well as the chemical shift of the C-2 methine proton at τ 5.3, are indicative of the 2,3-dihydro-4-pyridone structure **11** for the reduction product. These data are in excellent agreement with those reported[12] for 2,3-dihydro-2,6-diphenyl-4-pyridone. Hence, the structure of the adduct is **10**, suggesting that **6** is the adduct resulting from interaction of **2** with azirines **1a–d**.

Unequivocal proof was provided by an independent synthesis of **6a**. The experimental approach involved the cyclization of 1,2,5-triphenyl-1,3,5-pentanetrione (**12**) with ethanolic ammonia according to the procedure described by Light and Hauser[10b] for 1,5-disubstituted-1,3,5-pentanetriones.



1,2,5-Triphenyl-1,3,5-pentanetrione, for which structure **12** was reported,[13] was obtained by us in two forms (see Experimental Section). The initial form obtained was assigned a dienol structure (**13**) based on the observation of two enolic protons in the nmr spectrum.[14] A second form was obtained upon recrystallization of **13** from 95% ethanol.

Based on the observation of a strong 1680-cm^{-1} band in the infrared and the presence of two singlets in the olefinic region of the nmr spectrum, **14** is considered to be the most reasonable structure for this second form. Either **13** or **14** was converted with ammonia to pyridone **6a**, albeit in low yield (10%). The major product in both cases was identified through its nmr and mass spectra as the retro Claisen product 1,4-diphenyl-1,3-butanedione, in either of two enolic forms (**15** or **16**).

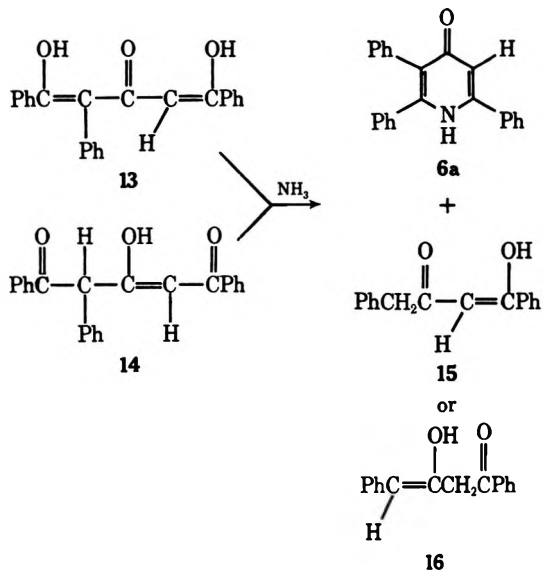
(10) (a) S. F. Mason, *J. Chem. Soc.*, 4874 (1957); L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958, p 207. (b) R. J. Light and C. R. Hauser, *J. Org. Chem.*, **25**, 538 (1960).

(11) The pathway involving C–C cleavage of the azirine and cycloaddition to give **3** is also unlikely on mechanistic grounds, because thermal excitation should result in preferential cleavage of the C–N bond, whereas C–C cleavage is usually the result of an electronically excited state.

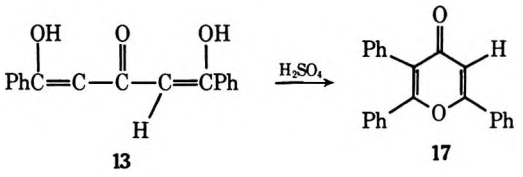
(12) N. Sugiyama, M. Yamamoto, and C. Kashima, *Bull. Chem. Soc. Jap.*, **43**, 902 (1970).

(13) M. Stavaux and N. Lozac'h, *Bull. Soc. Chim. Fr.*, 2082 (1967).

(14) This dienol structure is similar to that proposed by Light and Hauser for several related triketones; see ref 10b.



2,3,6-Triphenyl-4*H*-pyran-4-one (**17**) was obtained in high yield upon treatment of **13** with cold concentrated sulfuric acid in a manner described for other triketones.[10b] The nmr spectrum of **17** was found to be

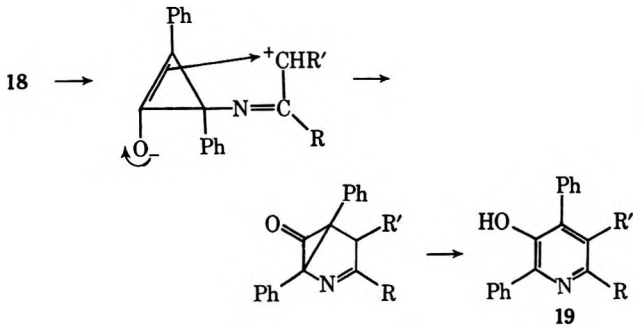


almost identical with that of pyridone **6a**, offering further confirmation of structure.

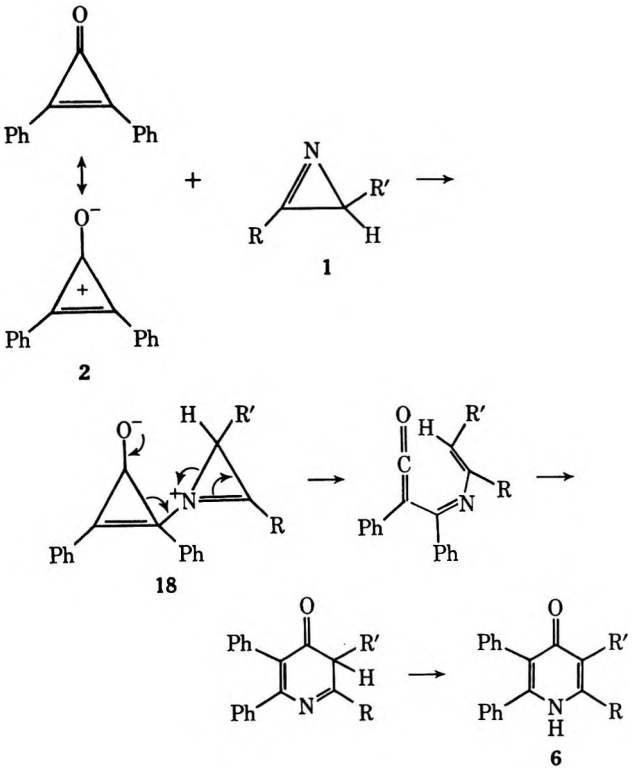
The results of the azirine cycloadditions are summarized in Table I.

The 4(1*H*)-pyridones **6** can be pictured as arising from the reaction of diphenylcyclopropenone (**2**) with substituted azirines (**1**) by way of nucleophilic attack of the weakly basic azirine nitrogen on the electrophilic cyclopropenone ring followed by an intramolecular Cope cyclization, as illustrated in Scheme II.[15a]

A possible competing reaction of intermediate **18**, analogous to a reaction described for the rearrangement of a norbornyl aziridine,[15b] should lead to a 3-hydroxy pyridine **19** and is therefore not occurring in this case.



SCHEME II



Experimental Section[16]

Reaction of 2-Phenylazirine (1a) with Diphenylcyclopropenone (2).—A solution of 2-phenyl-1-azirine (0.333 g, 0.0028 mol) and diphenylcyclopropenone (0.587 g, 0.0028 mol) in 23 ml of dry toluene was heated at reflux for 2 days. After this time, the solvent was evaporated and 25 ml of anhydrous ether was added to the residue. An insoluble white solid, **6a**, remained (0.250 g, 27% based on a 1:1 adduct):[17] mp 226–227° (unaffected by recrystallization from benzene–hexane); mass spectrum *m/e* (rel intensity) 323 (20.98, M^+), 322 [36.94, $(M-1)^+$], 178 (9.68, $PhC{\equiv}CPh^+$); ir ($CHCl_3$) 3500, 3400, 1625, 1580, 1555 cm^{-1}; nmr ($CDCl_3$) τ 3.05 (1 H singlet), 2.82, 2.77 (two 5 H singlets), 2.5 (5 H multiplet).

Anal. Calcd for $C_{23}H_{17}NO$: C, 85.42; H, 5.30; N, 4.33. Found: C, 85.47; H, 5.26; N, 4.15.

Reaction of 2-phenyl-3-methylazirine (1b) with 2 (0.0054 mol each) under reflux for 4 days led to 0.90 g (50% yield)[17] of pure **6b**: mp 251.5–252°; mass spectrum *m/e* (rel intensity) 337 (56.00, M^+), 336 [100, $(M-1)^+$], 178 (49.33, $PhC{\equiv}CPh^+$); ir ($CHCl_3$) 3400, 1625, 1580, 1550 cm^{-1}; nmr ($CDCl_3$) 7.93 (3 H singlet), 2.8, 2.73, 2.5 (three 5 H singlets, total aromatic region integrates for 16 H); uv (95% ethanol) λ_{max} 246 nm (ϵ 39,000); uv (0.13 *N* HCl–95% ethanol) λ_{max} 237 nm (ϵ 40,000).

Anal. Calcd for $C_{24}H_{19}NO$: C, 85.43; H, 5.68; N, 4.15. Found: C, 85.60; H, 5.83; N, 4.07.

Reaction of 2,3-diphenylazirine (1c) with 2 (0.0028 mol each) under reflux for 2 days gave 0.30 g (27% yield)[17] of pure **6c**: mp 330–331°; mass spectrum *m/e* (rel intensity) 399 (63.34, M^+), 398 [100, $(M-1)^+$], 178 (3.80, $PhC{\equiv}CPh^+$); ir (KBr) 3400, 3220, 1620, 1590, 1510 cm^{-1}; nmr (CH_3OD) τ 2.77 and 2.65 (singlets in 1:1 ratio).

Anal. Calcd for $C_{29}H_{21}NO$: C, 87.19; H, 5.30; N, 3.51. Found: C, 87.16; H, 5.34; N, 3.68.

Reaction of 2,3-diethylazirine (1d) with 2 (0.002 mol each) led after 3 days of refluxing to 0.2 g (33% yield)[17] of pure **6d**: mp 262–263°; mass spectrum *m/e* (rel intensity) 303 (66.64,

(15) (a) A pathway involving the trapping of a vinyl nitrene (a tautomer of the azirine **1**) by a dipolar ring-opened form of diphenylcyclopropenone (**2**) would also satisfy the results. At the present this path seems unlikely because heating of α-azidostyrene in benzene in the presence of **2** produced only azirine **1a** and no pyridone **6a**. (b) A. C. Oehlschlager and L. H. Zalkow, *J. Org. Chem.*, **30**, 4205 (1965).

(16) All melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer 457 spectrophotometer. Nmr spectra were recorded with a Varian A-60A spectrometer using tetramethylsilane as an internal standard. The elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(17) Examination of the alkyl region in the nmr spectrum of the ether-soluble material demonstrated the presence of starting azirine only.

M^-), 302 [100, $(M - 1)^+$], 178 (70.00, $PhC{\equiv}CPh^+$); ir (KBr) 3400, 3220, 1625, 1615, 1580, 1525 cm^{-1}; nmr (50% CD_3OD–$CDCl_3$) τ 8.83, 8.70 (two overlapping 3 H triplets), 7.35, 7.22 (two overlapping 2 H quartets), 2.86, 2.77 (two 5 H singlets).

Anal. Calcd for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62. Found: C, 83.05; H, 6.89; N, 4.58.

Reaction of 2-phenyl-3,3-dimethylazirine (9) with 2 (0.0028 mol each) under reflux for 2 days gave 0.35 g (35% yield)[18] of adduct **10**: mp 154.5–155.5° (unaffected by recrystallization from cyclohexane); mass spectrum *m/e* (rel intensity) 351 (100, M^+), 178 (99.12, $PhC{\equiv}CPh^+$); ir ($CHCl_3$) 1670, 1650, 1575, 1550 cm^{-1}; nmr ($CDCl_3$) τ 8.36 (6 H singlet), 2.82–2.15 (15 H multiplet).

Sodium Borohydride Reduction of 3,3-Dimethyl-2,5,6-triphenyl-4(3*H*)-pyridone (10).—Sodium borohydride (40 mg, 1.0 mmol) was added to a suspension of **10** (100 mg, 0.29 mmol) in 10 ml of absolute ethanol. Solution occurred immediately. After 18 hr at room temperature, the solvent was evaporated and the resulting white solid was treated with 10% aqueous ammonium chloride (10 ml). An ether extract (50 ml) was dried over $MgSO_4$, filtered, and evaporated to give 100 mg (100%) of a pale yellow solid: mp 216–217° (unaffected by recrystallization from benzene–hexane); mass spectrum *m/e* (rel intensity) 353 (100, M^+), 352 [25.40, $(M - 1)^+$], 178 (18.99, $PhC{\equiv}CPh^+$); ir ($CHCl_3$) 3400, 1625, 1580, 1550 cm^{-1}; nmr ($CDCl_3$) τ 8.9 (two 3 H singlets separated by 2 Hz), 5.3 (1 H doublet, J = 1.5 Hz, collapses to a singlet upon D_2O exchange), 4.85 (1 H, broad, disappears upon D_2O exchange), 2.95, 2.8, 2.6 (three 5 H singlets); uv (95% ethanol) λ_{max} 230 nm (ϵ 15,000), 345 (10,000); uv (0.7 NHCl–95% ethanol) λ_{max} 232 nm (ϵ 14,000) 347 (9000).

Anal. Calcd for $C_{25}H_{23}NO$: C, 84.95; H, 6.56; N, 3.93. Found: C, 84.72; H, 6.69; N, 3.94.

1,2,5-Triphenyl-1,2,5-pentanetrione (12).[13]—Under a dry nitrogen atmosphere, a solution of phenyl-2-propanone (13.4 g, 0.1 mol) and methyl benzoate (40.8 g, 0.3 mol) in 100 ml of dimethoxyethane (distilled from lithium aluminum hydride) was added to a stirred suspension of sodium hydride (50% oil dispersion, 24.0 g, 0.5 mol) in 300 ml of dimethoxyethane at reflux. The reaction mixture was refluxed for 5 hr, after which time the solvent was evaporated and 300 ml of diethyl ether was added to the pasty residue at 0°. Dropwise addition of cold water (200 ml) resulted in the formation of a bright yellow solid (30 g) which was insoluble in either the aqueous layer or the ethereal layer. This material was suspended in a two-phase mixture of saturated aqueous ammonium chloride (200 ml) and benzene (500 ml). After 3 days, solution was observed to have occurred. Evaporation of the benzene gave 26 g (65%) of bright yellow, hexane-soluble needles of **13** which did not exhibit a sharp melting point: mp 96–115°; ir ($CHCl_3$) 1510–1615 cm^{-1} (strong, broad); nmr ($CHCl_3$) τ 4.2 (1 H singlet), 2.9–2.35 (15 H multiplet), −3.1 (1 H singlet), −5.3 (1 H singlet).

(18) Examination of the alkyl region in the nmr spectrum of the ether-soluble material (0.65 g) demonstrated the presence of starting azirine and adduct in a 1:1 ratio. Based on this observation the actual conversion is 67%.

Recrystallization of **13** from 95% ethanol gave **14**, another tautomer of the triketone:[19] mp 110–112° (lit.[13] mp 105–108°); ir ($CHCl_3$) 1680, 1520–1620 cm^{-1}; nmr ($CDCl_3$) τ 4.23 (1 H singlet), 3.73 (1 H singlet), 2.85–2.45 (11 H multiplet), 2.25, 2.0 (two 2 H multiplets).

Cyclization of 1,2,5-Triphenyl-1,3,5-pentanetrione with Ammonia to Form 2,3,6-Triphenyl-4(1*H*)-pyridone (6a).[20]—To 1.0 g of 1,2,5-triphenyl-1,3,5-pentanetrione (either **13** or **14**) dissolved in 50 ml of absolute ethanol was slowly added commercial, anhydrous liquid ammonia until the flask was cold. The solution was evaporated to dryness, and the process was then repeated with the residue. Repeated recrystallization from benzene–hexane afforded **6a** as a white solid (0.1 g, 10%), mp 225–226°. The ir and nmr spectra of this material were identical with those of the adduct **6a** obtained from **2** and 2-phenylazirine. Nmr spectral analysis of the benzene–hexane-soluble fraction demonstrated the absence of starting triketone.

The hexane-soluble portion (0.60 g) had the following spectra: mass spectrum *m/e* 238 (M^+); ir ($CHCl_3$) 1500–1670 cm^{-1} (strong, broad); nmr ($CDCl_3$) τ 6.3 (2 H), 3.9 (1 H), 2.72 (5 H), 2.4 (5 H), −4.0 (1 H, broad). These spectral data indicate that the major product is an enol chelate form (either **15** or **16**) of 1,4-diphenyl-1,3-butanedione, resulting from a retro Claisen reaction. The material gave a crystalline copper chelate, mp 209–211° (lit.[21] mp 203–205°).

The Cyclization of Dienol 13 to 2,3,6-Triphenyl-4*H*-pyran-4-one (17).[18]—A 0.5-g sample of 1,2,5-triphenyl-1,3,5-pentanetrione (**13**) was dissolved in 10 ml of concentrated sulfuric acid at 0°. After 10 min at this temperature, the solution was poured into ice water. The resulting precipitate was collected on a funnel, washed with water, and recrystallized from benzene–hexane to give a white solid (0.35 g, 70%): mp 174.5–175°; mass spectrum *m/e* (rel intensity) 324 (58.48, M^+), 323 [100, $(M - 1)^+$], 178 (32.28, $(PhC{\equiv}CPh^+)$; ir ($CHCl_3$) 1645, 1635, 1610, 1595 cm^{-1}; nmr ($CDCl_3$) τ 2.9 (1 H singlet), 2.75, 2.7 (two 5 H singlets), 2.35 (5 H multiplet).

Anal. Calcd for $C_{23}H_{16}O_2$: C, 85.16; H, 4.97. Found: C, 85.09; H, 4.86.

Registry No.—**2**, 886-38-4; **6a**, 33707-15-2; **6b**, 33666-41-0; **6c**, 33707-16-3; **6d**, 33666-42-1; **10**, 33707-17-4; **11**, 33815-38-2; **13**, 33707-18-5; **17**, 33707-19-6.

Acknowledgment.—Support of this work by Public Health Service Grant CA-04474 from the National Cancer Institute is gratefully acknowledged.

(19) This is evidently the form reported by Stavaux and Lozac'h; see ref 13.

(20) Patterned after the general procedure described by Light and Hauser; see ref 10b.

(21) K. G. Hampton, T. M. Harris, and C. H. Hauser, *J. Org. Chem.*, **29**, 3511 (1964).

Carbon-13 Magnetic Resonance. Chemical Shift Additivity Relationships in *N*-Methyl-4-piperidones

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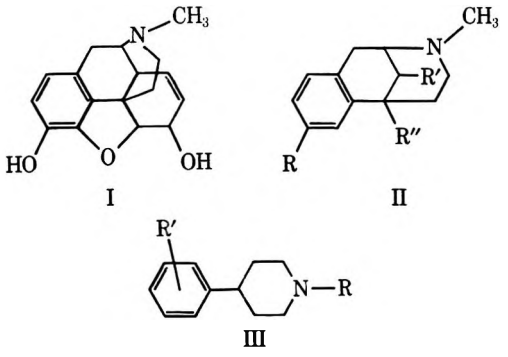
Received December 13, 1971

Natural abundance carbon-13 spectra of a series of substituted 4-piperidones (and some pertinent piperidines) in free base, hydrochloride, and methiodide salt forms have been determined and the observed chemical shifts analyzed in terms of the conformational properties of the molecules. Additivity parameters have been derived for the substituents and are compared with similar parameters obtained for the methylcyclohexanes, cyclohexanones, and 1,3-dioxanes. The reduced magnitude of the substituent parameters in the present series compared with the cyclohexanes has been attributed to the higher degree of substitution in the ring, since the electronegative N—H and C=O centers are also considered as substituents in the cyclohexane system. Of particular importance are the additivity effects obtained on protonation and methiodation of the nitrogen in these systems. It is suggested that the parameters derived in this study will be valuable in determining stereo-structural activity relationships in the analgesics which may be readily derived from their precursors studied here.

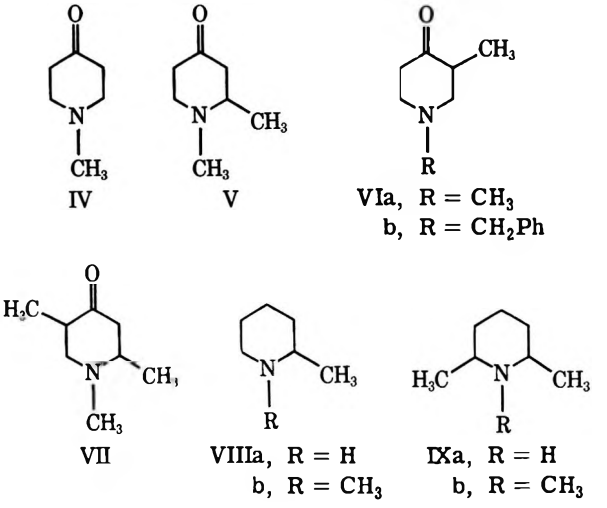
It has been shown that the stereoisomeric forms of many pharmacologically active molecules, which are simple derivatives of morphine (I), differ greatly in their anaigesic potency.[2,3]



I II III

It is, therefore, of considerable interest to determine the nature of stereo structural–activity relationships in these types of molecules. Studies concerned with these relationships have employed a variety of accepted methods for structural determination, the most generally useful of which has been proton magnetic resonance (pmr) spectroscopy as indicated by the work of Casy and coworkers.[4-10] Using pmr techniques it has been shown that conformation is a particularly important factor in the determination of the analgesic properties in, for example, the 6,7-benzomorphans (II)[6] and a variety of 4-phenylpiperidine derivatives (III).[4,5]

The purpose of the present paper is in part to suggest that the carbon-13 magnetic resonance (^{13}C nmr) technique may also be of considerable value in the determination of conformation in pharmacologically important molecules, particularly in cases where limited resolution of the proton multiplets in the pmr spectra is observed. Recent successes in the application of ^{13}C nmr spectroscopy in conformational analysis of the methylcyclohexanes,[11] the decalins,[12] the perhydroanthracenes and phenanthrenes,[13] the cyclohexanols and derivatives,[14] carbohydrates,[15] the 1,3-dioxanes,[16,17] some cyclic phosphonites,[18] and selected piperidines[19,20] justify this application. We have chosen to demonstrate the potential of the ^{13}C nmr technique for conformational analysis of pharmacologically active molecules by selecting a series of their synthetic precursors, the *N*-methyl-4-piperidones (IV–VII), and related



IV V VIa, R = CH_3; b, R = CH_2Ph

VII VIIIa, R = H; b, R = CH_3 IXa, R = H; b, R = CH_3

compounds VIII and IX along with their hydrochlorides and methiodides.

The conformational features of the *N*-alkyl-4-piperidones to be discussed have been defined using other techniques.[8-10] Consequently, we will use these results to confirm the general trends observed in the present

(1) Department of Pharmacy, Faculty of Pharmacy, Riyadh University, Riyadh, Kingdom of Saudi Arabia.

(2) *E.g.*, N. B. Eddy and E. L. May in "Synthetic Analgesics," Part IIB, Pergamon Press, Oxford, 1956.

(3) *E.g.*, A. H. Beckett and A. F. Casy, *J. Pharm. Pharmacol.*, **6**, 986 (1954).

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(8) M. M. A. Hassan and A. F. Casy, *ibid.*, **26**, 4517 (1970).

(9) M. M. A. Hassan and A. F. Casy, *Org. Magn. Resonance*, **1**, 389 (1969).

(10) M. M. A. Hassan and A. F. Casy, *ibid.*, **2**, 197 (1970).

(11) D. K. Dalling and D. M. Grant, *J. Amer. Chem. Soc.*, **89**, 6612 (1967).

(12) D. K. Dalling, D. M. Grant, and L. F. Johnson, *ibid.*, **93**, 3678 (1971).

(13) D. K. Dalling and D. M. Grant, private communication.

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(16) A. J. Jones, E. L. Eliel, D. M. Grant, M. C. Knoeber, and W. G. Bailey, *ibid.*, **93**, 4772 (1971).

(17) F. G. Ridell, *J. Chem. Soc. B*, 331 (1970); G. M. Kellie and F. G. Ridell, private communication.

(18) W. G. Bentrude, K. C. Yee, R. D. Bertrand, and D. M. Grant, *J. Amer. Chem. Soc.*, **93**, 797 (1971).

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(20) W. O. Crain, Jr., W. C. Wildman, and J. D. Roberts, *J. Amer. Chem. Soc.*, **93**, 990 (1971).

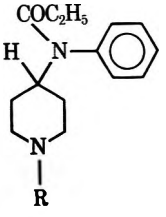
Table I

Carbon-13 Chemical Shifts in *N*-Alkyl-4-piperidones[a]

Structure	Form	Solvent	Carbon position C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	C-3′ or C-5′
IV		Neat	55.40	40.89	206.22	40.89	55.40	45.14		
IV	HCl	$CHCl_3$	52.03	38.39	203.08	38.39	52.03	42.20		
IV	CH_3I	DMSO	60.58	35.92	201.65	35.92	60.58	51.83		
IV	CH_3I	H_2O	61.11	33.12	101.72	33.12	61.11	52.09		
V		Neat	58.81	48.88	207.29	41.38	54.87	41.59	19.69	
V	HCl	$CHCl_3$/DMSO[b]	58.68	44.60	202.47	37.29	51.80	(~39.5)	17.30	
V	CH_3I	DMSO	65.88	42.89	201.07	35.57	60.93	57.82 46.21	14.94	
V	CH_3I	H_2O	66.20	42.89	89.90	35.57	62.44	52.87	14.40	
VIa		Neat	63.40	43.83	207.77	40.57	56.20	45.10		11.89
VIa	HCl	$CHCl_3$	60.44	40.74	203.81	37.34	53.09	43.10		10.89
VIa	CH_3I	DMSO	65.75	38.58	203.56	35.60	61.10	55.53 48.29		10.78
VIa	CH_3I	H_2O	67.00	39.40	92.75	35.94	62.27	56.98 49.54		11.00
VIb		Neat	61.41	40.41	207.89	43.75	60.53	(53.41)[c]		11.93
VIb	HCl	$CHCl_3$	56.30	37.25	204.00	40.75	60.36	(51.17)[c]		11.00
VIb	CH_3I	$CHCl_3$	63.94	35.69	203.81	36.68	70.18	58.12 (59.01)[c]		10.95
VII		Neat[d]	59.78	48.60	207.41	44.03	63.95	41.04	20.84	11.14
VII	HCl	$CHCl_3$	59.82	45.46	203.30	41.48	60.89	39.93	17.90	10.66
VII	CH_3I	DMSO	67.18	42.96	203.40	39.22	67.18	53.02 51.66	15.60	10.66
VII	CH_3I	H_2O	67.00	43.06	92.31	39.88	68.07	54.00	15.54	10.72

[a] Given in parts per million downfield relative to TMS. [b] Low solubility necessitated use of mixed solvent. C-1′ line obscured by solvent peak. [c] Parentheses indicate that this is the shift for the methylene carbon in the benzyl derivatives. Phenyl ring carbons were found at 138.53 (α-C), 128.70 (*o*-C), 128.30 (*m*-C), and 127.11 ppm (*p*-C) in the free base VIb, and at 129.60 (α-C), 130.71 (*o*-C), 128.53 (*m*-C), and 127.37 ppm (*p*-C) in its hydrochloride. The phenyl ring region in the methiodide of VIb was not investigated. [d] It has been shown (ref 10) that VII exists as an approximately 90:10 equilibrium mixture in which the major isomer has the *trans*-2,5-dimethyl configuration with the *N*-methyl group equatorial. These results are for the major isomer.

work. Currently we are attempting to apply the fundamental data derived herein and have obtained some success in the conformational analysis of several 4-phenylpiperidine and fentanyl type (X) analgesics,



X

which are derived from the above piperidones. This work will be the subject of further publications.

Experimental Section

Carbon-13 spectra were determined using a Varian Associates HA-100D-15 spectrometer operating at 25.14 MHz. For carbon-13 determinations this instrument features a Varian V-3530 rf/af sweep unit. Fixed frequency audio modulation for the signal oscillator was obtained from a Hewlett-Packard 5100B–5110B frequency synthesizer system. Broad-band proton decoupling at approximately 100 MHz was achieved using a Varian V3512-1 heteronuclear decoupler. Frequency swept spectra were obtained by applying pulses from the digital recorder to drive a Varian C-1024 time averaging device and the rf sweep. Where long-term spectral accummulation was necessary, the C-1024 was used in the internal trigger mode. The sweep width (2.0–2.5 KHz) was calibrated using a Hewlett-Packard 3735 electronic counter and measured to ±0.25 Hz end to end. All samples were contained in precision-ground 12-mm-o.d. tubes, and a 5-mm capillary containing carbon-13 enriched methyl iodide was added to provide the lock signal.

The majority of compounds studied were freshly prepared and purified by techniques previously described.[8-10] The parent *N*-alkyl compounds were run as neat liquids containing 10% tetramethylsilane (TMS) as internal reference. Their hydrochlorides were studied as solutions in chloroform, also containing TMS as reference, and the methiodides in freshly distilled *dry* dimethyl sulfoxide which also served as reference. (TMS–DMSO, 41.17 ppm.) Solutions of the methiodides in water produced the geminal diols of the 4-piperidones as described in the literature.[8-10] In these cases 10% *p*-dioxane was added as internal reference (TMS–dioxane, 67.12 ppm). In all cases chemical shifts were calculated relative to TMS.

Results

The observed carbon-13 chemical shifts in the *N*-alkyl-4-piperidones IV–VII and their hydrochlorides, methiodides, and, where appropriate, their 4,4-*gem*-diol derivatives, are presented in Table I. Supporting data on 1,2-dimethyl- (VIII) and 1,2,6-trimethylpiperidine (IX) and their hydrochlorides and methiodides are given in Table II. For comparison, data on 2-methyl- (VIIIa) and 2,6-dimethylpiperidine (IXa) are also given in Table II. The choice of solvents shown in Tables I and II was dictated by the solubility of the various species and enabled comparison with the earlier proton data.[8-10] In general solvent effects on carbon-13 chemical shifts are considered sufficiently small (~0.5 ppm) to be insignificant[11-19] unless conformational changes occur in different solvents. The earlier pmr studies[8-10] indicate that no conformational changes occur in the systems presently being described.

Assignment of the carbon-13 resonances to the appropriate carbon position in the compounds studied was made using conventional techniques.[21] In the

(21) See, for example, A. J. Jones, D. M. Grant, and K. F. Kuhlmann, *J. Amer. Chem. Soc.*, **91**, 5013 (1969), and ref 16.

TABLE II

CARBON-13 CHEMICAL SHIFTS IN 2-METHYL- AND 2,6-DIMETHYLPIPERIDINES[a]

Structure	Form	Solvent	Carbon position C-2	C-3	C-4	C-5	C-6	C-1′	C-2′ or C-6′
VIIIa		Neat	53.37	35.99	26.33	27.48	48.20		24.02
VIIIb		Neat	59.30	34.76	24.98	26.41	57.03	42.99	20.24
VIIIb	HCl	$CHCl_3$	61.45	31.54	22.15	23.39	56.04	41.00	17.86
VIIIb	CH_3I	DMSO	69.75	29.74	22.09	23.20	67.01	55.31	16.81
								44.18	
IXa		Neat	52.74	34.48	25.41	34.48	52.74		23.35
IXb		Neat	59.54	35.28	25.02	35.28	59.54	37.86	21.83
IXb[b]	HCl	$CHCl_3$	61.69	31.86	22.27	31.86	61.69	36.39	18.30
IXb	CH_3I	DMSO	70.62	28.98	22.86	28.98	70.62	50.23	16.57
								36.07	

[a] Given in parts per million downfield relative to TMS. [b] Studied as a mixture. The minor isomer (*ca.* 30%) exhibited resonances at 59.50 (C-2,6), 24.74 (C-3,5), 24.32 (C-4), 31.86 (C-1′), and 17.46 ppm (C-2′, 6′).

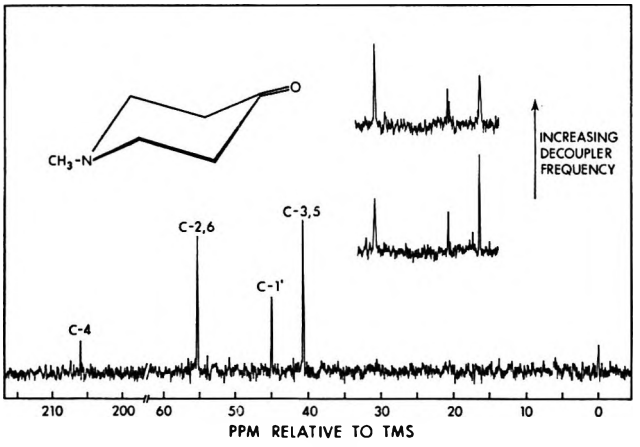


Figure 1.—The natural abundance carbon-13 magnetic resonance spectrum of *N*-methyl-4-piperidone (IV). Insets show the effects of stepping the ^1H decoupler frequency in the selective decoupling experiment.

symmetrical molecules, *N*-methyl-4-piperidone (IV) and 1,2,6-trimethylpiperidine (IXb), the double intensity of the resonances due to the equivalent carbons C-2,6, C-3,5, and C-2′,6′ (where *n*′ refers to the substituent carbon at the appropriate position *n* on the piperidine ring) enabled their distinction compared with the single intensity of the resonances due to C-1′ and C-4. The distinction of C-4 from C-1′ in the piperidones arises from observation of the typical low-field carbonyl shift (~204 ± 3 ppm) at C-4. In IXb the off-resonance decoupled spectrum exhibited a triplet about the higher field resonance of the pair attributable to C-1′ or C-4 and a quartet about the highest field resonance (21.8 ppm) attributable to the C-2′,6′ methyl carbon atoms. The carbon-13 spectrum of *N*-methyl-4-piperidone (IV) is shown in Figure 1. Figure 1 also shows the results of a selective decoupling experiment which established the order of the chemical shifts given in Table I for the compound IV.

For purposes of assignment the remaining molecules in this study (V–VII in Table I and VIII in Table II) form a second group which due to the absence of symmetry exhibits carbon-13 resonances of approximately equal intensity for each of the carbon atoms in the molecule. Many of the spectral assignments for these methyl-substituted systems were first suggested from substituent parameter considerations and were then confirmed where possible using off-resonance or selective proton decoupling techniques.

An additional factor, which aided the assignments for all bases was the consistent trend observed in the carbon-13 resonances on protonation or methiodation. Approximate parameters for the effects of protonation and for methiodation were also used in the initial interpretation of the spectra of the corresponding derivatives. Some precedence for this approach was set in the work of Duch and Grant[19] on the piperidine hydrochlorides. With only minor exceptions the results given in Tables I and II add further validity to this procedure.

All further assignments were made in a relatively routine manner and do not warrant detailed discussion.

Discussion

In the previous section attention has been focussed on the use of additivity relationships to provide a mechanism for initial spectral interpretation in systems related by structure and conformation. Spectroscopic methods were used to confirm many of the suggested assignments. The overall objective is to provide a set of general and reliable additivity parameters which would provide a direct mechanism for determining structure and conformation for any particular class of molecules.

The carbon-13 additivity relationships derived from the methylcyclohexanes by Dalling and Grant[11] have provided a most important foundation for studies concerned with structure and conformation in compounds containing saturated six-membered rings. A number of recent applications[12-19,22] have used these parameters in assigning carbon-13 spectra of relatively complex molecules. It has become increasingly clear from the observed trends that additional or modified parameters are valuable in systems containing substituted cyclohexanes. Introduction of an electronegative but isoelectronic NH- group in place of a CH_2 group, as in the piperidines, appreciably changes the local charge density of the adjacent carbon atoms.[23] The consequent deshielding, in comparison with the alicyclic analogs, is apparent from the downfield shift (20.6 ppm) at C-2,6 in piperidine compared with cyclohexane.[11,19,20] In the 4-piperidones similar effects are expected as a consequence of the relatively electronegative carbonyl group at C-4. The adjacent (α-C) carbon atoms C-3,5 shift downfield 14.7 ppm in *N*-

(22) H. J. Reich, M. Jautelat, M. J. Messe, F. J. Weigert, and J. D. Roberts, *J. Amer. Chem. Soc.*, **91**, 7445 (1969).

(23) G. E. Maciel and G. B. Savitsky, *J. Phys. Chem.*, **69**, 3925 (1965).

methyl-4-piperidone[24] compared with *N*-methylpiperidine.[19,20] This downfield shift is similar to that noted at the α carbon in cyclohexanone (13.6 ppm)[25] compared with cyclohexane[11] and may be considered characteristic for an α-C-carbonyl substituent effect. The chemical shifts of the carbonyl at C-4 (204 ± 3 ppm) and other cyclanones (211 ± 4 ppm)[26] are similar but differ from that of the carbonyl carbon in the 2-piperidones (170 ± 3 ppm).[27] This latter value has been noted in several nucleoside bases[28] and is indicative of the amide character of these carbon atoms.

The effect of methyl substitution has been characterized in the methylcyclohexanes,[11,13] selected piperidines,[19] and some 1,3-dioxanes.[16,17] Table III provides a summary of the average substituent shifts (for methyl and other substituents relevant to the present discussion) observed in most of the six-membered ring systems studied to date. This summary is by no means comprehensive, and the paucity of data coupled with solvent shifts suggests that these parameters are accurate to one significant figure. However, for a given series of compounds it is determination of the order more than the absolute magnitude of the calculated shifts that is of primary significance in the use of these parameters. Downfield shifts of approximately 6.0 ppm are observed at the carbon site at which equatorial methyl substitution occurs, while concomitant downfield shifts of 9.0 ppm are found at the adjacent β position in the methylcyclohexanes.[11] Shifts of carbon atoms further removed from the site of substitution are sufficiently small to be neglected. Substitution of a methyl group at C-3 (≡C-5) in the *N*-methyl-4-piperidones VIa and VII results in an average downfield C-α_e shift of only 3.0 ppm. The corresponding shift at C-2 in the 4-piperidone V is 3.4 ppm, while in the model piperidine systems VIIIb and IXb the average downfield shift at C-2 is 2.7 ppm compared with *N*-methylpiperidine.[19,20] In 1,2,5-trimethyl-4-piperidone (VII) the C-α value is 4.38 ppm. These values provide an average C-α_e methyl substituent shift of only 3.7 ppm as given in Table III. Sizable terms are required to correct the cyclohexane C-α_e parameter where substitution occurs at a carbon site adjacent to a higher order (tertiary or quaternary) substituted center such as carbonyl. Similar correction terms were considered necessary to account for the chemical shifts in the branched alkanes compared with their linear analogs.[29] In general, the 6.0-ppm C-α_e substituent parameter in the methylcyclohexanes may be reduced to 2.5 ppm when substitution occurs adjacent to higher order substituted centers.[30] A correction term for C-α_e near to −3.0 ppm seems appropriate where this center is carbonyl, while approximately −1.5 ppm would seem appropriate to the NH group. The relative magnitude of these two correction terms also invalidates the possibility that the electronegativity of the adjacent center attenuates the C-α_e parameter. The low C-α_e value (2.7 ppm) in VII, VIIIb, and IXb presumably arises since steric interactions between the 1- and 2-methyl groups would raise the chemical shift at C-2 and consequently compensate for the lowering *via* the substituent effect.

TABLE III

SUBSTITUENT PARAMETERS OBSERVED IN SIX-MEMBERED RING ALICYCLICS AND DERIVATIVES[a]

	Substituent parameter derived from				
Substituent	Cyclohexanes (ref 11, 13)	Cyclohexanones (ref 25)	1,3-Dioxanes (ref 16, 17)	Piperidines (ref 19, 20 and present work)	4-Piperidones (present work)
$NH_{C-\alpha}$[b]				20.6	(20.6)
$C{=}O_{C-\alpha}$[b]		13.3			14.7
$CH_{3C-\alpha_e}$[b]	5.96	5.4	4.6	5.4	3.7
$CH_{3C-\beta_e}$[b]	9.03	8.2	6.7	8.5	7.9
$CH_{3C\gamma-a}$[b]	4.5		7.5		
$NCH_{3C-\beta_e}$[b]				8.9[d]	(8.9)
$CH_3NH_{C-\alpha}$[+c]				−2.5[e]	−3.1[e]
$CH_3NH_{C-\beta}$[+c]				−4.9	−2.8
$CH_3NH_{C-\gamma}$[+c]				−3.5	−3.7
$CH_3NCH_{3C-\alpha}$[+c]				10.5[d]	4.6
$CH_3NCH_{3C-\beta}$[+c]				−4.8[d]	−4.9
$CH_3NCH_{3C-\gamma}$[+c]				−2.5[d]	−4.3

[a] Given in parts per million. Negative sign indicates upfield shift. [b] Parameter derived with respect to cyclohexane. [c] Parameters derived with respect to free base. [d] Derived from data obtained in the present work. [e] Parameter does not include data from 2-methyl derivatives in which opposite effects were observed.

The C-β_e parameter observed in the methylcyclohexanes (9.0 ppm)[11,13] is attenuated by an adjacent carbonyl or piperidine–nitrogen center. The C-β_e value given in Table III for the 4-piperidones does not include the C-β_e contributions observed at C-4 in the 3-methyl- (VIa) and 1,2,5-trimethyl-4-piperidone (VII), where the carbonyl carbon is shifted downfield 1.32 ppm relative to *N*-methyl-4-piperidone (IV). This shift is close to the corresponding β-carbonyl site in 2-methylcyclohexanone (downfield, 1.5 ppm)[25] compared with cyclohexanone. These modified C-β shifts suggest that the carbonyl oxygen compensates for the lowering in electron density at the carbonyl carbon by donating electrons when methyl (or alkyl) substitution occurs at adjacent sites. This may be a mechanism by which the C-α and C-β methyl substituent parameters are generally lowered in the presence of electronegative centers. The C-β_e parameter follows the same trends in *N*-methyl and *C*-methyl derivatives. Thus the shifts at C-2 or C-6 in *N*-methylpiperidine,[19,20] 1,2-dimethylpiperidine (VIIIb), and 1,2,6-trimethylpiperidine (IXb) give an average C-β_e parameter of 8.9 ppm. This parameter may be the same in the 4-piperidones, though in the *N*-methyl-2-piperidones[27] it is approximately 5 ppm.

The effect of the carbonyl group and the *N*-methyl group on the methyl shifts in the compounds studied also warrants consideration. The difference in shift (9.5 ppm) between the 2- and 3-methyls in V, VIa, VIb, and VII is partly attributable to the carbonyl group, since in the piperidines VIII and IX the methyl shifts at C-2′ correspond (approximately 20 ppm relative to TMS) to those in the 2-methyl-4-piperidones. A similar difference (9.0 ppm) was noted for the methyl shift

(24) 4-Piperidone is too unstable to enable spectral determination; hence the shift difference quoted above is for the *N*-methyl derivatives.

(25) F. J. Weigert and J. D. Roberts, *J. Amer. Chem. Soc.*, **92**, 1347 (1970).

(26) J. B. Stothers and P. C. Lauterbur, *Can. J. Chem.*, **42**, 1563 (1964).

(27) A. J. Jones, unpublished results.

(28) A. J. Jones, D. M. Grant, M. W. Winkley, and R. K. Robins, *J. Amer. Chem. Soc.*, **92**, 4079 (1970); *J. Phys. Chem.*, **74**, 2684 (1970).

(29) D. M. Grant and E. G. Paul, *J. Amer. Chem. Soc.*, **86**, 2984 (1964).

(30) Note that contributions from the carbonyl group on the carbon-13 shift at C-2 in the *N*-methyl-4-piperidones are neglected, since the difference in shift observed for the corresponding positions in cyclohexanone compared with cyclohexane is only −0.3 ppm.

in 2-methylcyclohexanone compared with other methylcyclohexanones[25] and it was suggested that the eclipsing of the 2-methyl and the carbonyl group in the 2-methyl derivative probably gave rise to this difference. From 2-methyl- and 2,6-dimethylpiperidine (VIIIa and IXa) and their *N*-methyl derivatives VIIIb and IXb, it is clear that the *N*-methyl group causes an upfield shift (average, 2.6 ppm) at the 2-methyl carbon as a consequence of steric interactions between these equatorial groups. Similarly, the *N*-methyl group is shifted upfield an average of 4.1 ppm, as indicated in comparing *N*-methyl-4-piperidone (IV) with 1,2-dimethyl- (V) and 1,2,5-trimethyl-4-piperidone (VII). Such steric shifts have been clearly established in the methylcyclohexanes[11,13] and the 1,3-dioxanes[16,17] and their magnitude has in part been related to the interatomic distances between the interacting sites.[31]

In analyzing the data in Tables I and II in relation to N-methylation, one minor anomaly remains. The C-3 and C-5 shifts in 1,2-dimethylpiperidine (VIIIb) are upfield 1.1 ppm of those in 2-methylpiperidine (VIIIa) while in the *N*-methyl compound IXb (compared with IXa) these shifts are of similar magnitude but in the opposite direction. No reasonable explanation of this effect is apparent.

The effects of protonation and methiodation in the piperidines and 4-piperidones follow additive trends. Table III summarizes the average protonation parameters obtained by Duch and Grant[19] from piperidine and 2-, 3-, and 4-methylpiperidine and similar parameters for the 4-piperidones. Relatively large changes occur for all sites in the molecule and in general all shifts are upfield. The C-2,6 position provides the only exception to these upfield shifts, noticeably in cases where this position is methyl substituted in the protonated series, though invariably in the methiodide series. The $CH_3NH_{C-\alpha}^+$ parameter given in Table III does not include data for the 2-methyl-substituted piperidines and piperidones. Because quaternization changes the charge at the nitrogen by one electron, the observed effects of protonation or methiodation are remarkably small. The 3–4 ppm observed change represents at most only 2% of the total change possible on addition or subtraction of an electron to the molecular framework.[32] The nitrogen atom probably accounts for most of the charge effect from protonation or methiodation. The electrostatic effect of the positive nitrogen center will be to attract electrons from the carbon framework. Negative charge will build up at C-2,6 and will probably result in an upfield shift of these resonances. However, all C-3,5 and C-4 resonances shift upfield, suggesting buildup of electron charge at these sites also. The effect at C-3,5 can be reconciled by recognizing that the quaternizing substituent takes up the axial position on the nitrogen in the favored chair conformations of most of the piperidines and piperidones studied. Syn-axial 1,3 steric interactions will occur between the axial substituent at the nitrogen and the methylene protons at C-3,5, and upfield shifts commonly found in other molecules[11,16] will occur at these sites. In the minor isomer of the 1,2,6-trimethylpiperidine hydrochloride (IXb) (see footnote *a*, Table II) in which nitrogen inversion has occurred and the *N*-methyl group is now axial the C-3,5 and *N*-methyl carbons are shifted 7.2 and 4.5 ppm upfield, respectively. The greater steric interference of the methyl group is emphasized. No such steric interactions are likely to occur at C-4 or its substituents in any of the systems studied and it seems unlikely that direct charge-induced effects would be established over the molecular framework. Protonation of the carbonyl oxygen in the 4-piperidones IV–VII could shift the carbon-13 resonance upfield but similar upfield shifts observed in the piperidines VIII and IX exclude this explanation for the shifts at C-4. The shifts at C-4 in the quaternary nitrogen systems present an anomaly when compared with the cyclohexanes.[11,13] Duch and Grant[19] have used an electrostatic field calculation similar to that used by Horsley and Sternlicht[33] to explain the observed effect at C-4 with some degree of success. The similarity in the $CH_3NH_{C-\gamma}^+$ parameter between the piperidines[19] and 4-piperidones suggests that the effects at C-4 have the same origin and the electric field model provides an acceptable account of the C-4 shifts in these systems. A similar field effect has been invoked to explain the significantly greater $\nu_{C=O}$ stretching frequencies of the hydrochloride salts compared with those of the free bases in the 4-piperidones.[34]

In the 2-methylpiperidones V and VII and piperidines VIII and IX, protonation causes either a negligible or opposite shift (downfield 2.2 ppm) at C-2 compared with the unsubstituted or 3-methyl-substituted systems. From these shift effects it is apparent that the steric interaction between the 2-methyl group and the introduced axial proton results in an inductive effect at C-2 which compensates for the buildup of electron charge at C-2,6 upon protonation. The steric interaction described has been analyzed by Woolfenden and Grant[35] and is further emphasized by the upfield shift (average, 2.95 ppm) of the 2-methyl group in the protonated 2-methyl derivatives studied. On protonation the carbons C-1′ (equatorial *N*-methyl) and C-3′ are shifted upfield 1.76 and 0.80 ppm compared with the corresponding neutral systems. The effects at C-1′ are also presumably steric in origin. In the hydrochloride of *N*-benzyl-3-methyl-4-piperidone (VIb) the shift at C-2 is relatively small, while the α-carbon shift in the benzene ring is upfield 8.9 ppm, presumably because of conjugative interaction between the benzyl group and the nitrogen atom.

From Table III it is clear that in the methiodides of the 4-piperidones or the piperidines the axial methyl substituent at the nitrogen results in a downfield shift (5–10 ppm) at C-2,6, while the shifts for all other carbons are upfield. The parameters given in Table III are for the methiodides compared with the neutral system. The C-α parameter derived from the C-2,6 shifts in the methiodides provides us with an interesting test of the relationships so far derived. If the differ-

(31) The possibility that the magnitude of these shifts may depend on the electronegativity of intervening or adjacent atoms has not been excluded. We thank the referee for bringing this point to our attention.

(32) This argument is based on the general observation that carbon-13 shifts follow the linear relationship between shift and charge which involves a constant 160–200 ppm per electron. See, for example, H. Spiesecke and W. G. Schneider, *Tetrahedron Lett.*, 468 (1961).

(33) W. J. Horsley and H. Sternlicht, *J. Amer. Chem. Soc.*, **90**, 3738 (1968).

(34) A. F. Casy, private communication.

(35) W. R. Woolfenden and D. M. Grant, *J. Amer. Chem. Soc.*, **88**, 1496 (1966).

ence between a methiodide and a corresponding protonated system is an axial methyl substituent then an axial methyl β-substituent parameter at C-2,6 can be derived. In the 4-piperidones an average downfield shift of 7.1 ppm is derived while in the piperidines the corresponding value is 8.1 ppm. The $CH_3NCH_{3\,C\text{-}\alpha}{}^+$ parameter given in Table III for the piperidines (10.5 ppm) was derived from the data on the methiodides of 1,2-dimethyl- (VIII) and 1,2,6-trimethylpiperidine (IX) and consequently comprises an effect from the *N*-methyl-axial substituent (8.1 ppm) and the C-2′ methyl effect for the hydrochlorides (2.2 ppm). The sum of these values (10.3 ppm) is remarkably close to the composite value (10.5 ppm) as given in Table III. Similarly, in the piperidones the corresponding value (4.6 ppm) comprises the axial β-substituent effect (7.1 ppm) and the "charge effect" at C-2,6 (−3.1 ppm) providing the sum 4.0 ppm, also in close agreement with the composite value. These summations add further justification to the parameterization procedure suggested by the results of the present work. The effects of methiodation at the C-3,5 and C-4 sites follow similar trends to the hydrochlorides, though their magnitudes are greater. Further effects are also apparent at the substituent methyl carbons. The *N*-methyl carbons are found downfield 11.2 and 2.1 ppm, on the average, compared with the *N*-methyl carbon in the neutral molecule, while the shift at C-2′ in the 2-methyl-4-piperidones is shifted upfield an average of 4.6 ppm on methiodation. This latter shift is presumably steric in origin (see ref 35). A similar shift effect at C-3′ in the hydrochlorides (0.8 ppm) of the 3-methyl-4-piperidones VI and VII is also observed in the methiodides (0.9 ppm) and is also attributed to the steric effects.

The methiodides of substituted 4-piperidones are generally hydrolyzed in aqueous solution.[9,10] The carbon-13 shifts of the resulting geminal diols are given in Table I and although the upfield shift (approximately 100 ppm) at C-4 is clearly indicative of the change from a carbonyl to a geminal diol center no trends are clear for the other ring carbons.

Conclusions

The substituent additivity parameters summarized in Table III, in addition to the considerations outlined in the Discussion section, should provide a useful basis for the analysis of structure and conformation in more complex molecules. In subsequent studies, to be published, we have used these parameters with some success in order to determine conformations in a series of synthetic analgesics.[36]

Registry No.—IV, 1445-73-4; IV HCl, 34737-83-2; IV CH_3I, 34737-84-3; V, 13669-32-4; V HCl, 34737-86-5; V CH_3I, 34737-87-6; VIa, 4629-80-5; VIa HCl, 4629-76-9; VIa CH_3I, 34737-88-7; VIb, 34737-89-8; VIb HCl, 26822-34-4; VIb CH_3I, 34737-91-2; VII, 20281-02-1; VII HCl, 29849-51-2; VII CH_3I, 34737-92-3; VIIIa, 109-05-7; VIIIb, 671-36-3; VIIIb HCl, 5072-43-5; VIIIb CH_3I, 34737-95-6; IXa, 504-03-0; IXb, 669-81-8; IXb HCl, 5072-29-7; IXb CH_3I, 34737-99-0.

Acknowledgments.—This work was supported in part by the National Research Council of Canada, Grant A6416. We thank the referee for some helpful comments and Mr. Glen Bigam for spectrometer maintenance.

(36) *E.g.*, A. J. Jones, A. F. Casy, and K. M. J. McErlane, *Tetrahedron Lett.*, 1727 (1972).

Synthesis and Mass Spectra of Some 2-Carbomethoxy-2-carbomethoxymethyl-2,3-dihydro-4(1*H*)-quinazolinones

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A synthesis of 2-carbomethoxy-2-carbomethoxymethyl-2,3-dihydro-4(1*H*)-quinazolinones is described and the major electron impact fragmentation pathways of this series are discussed.

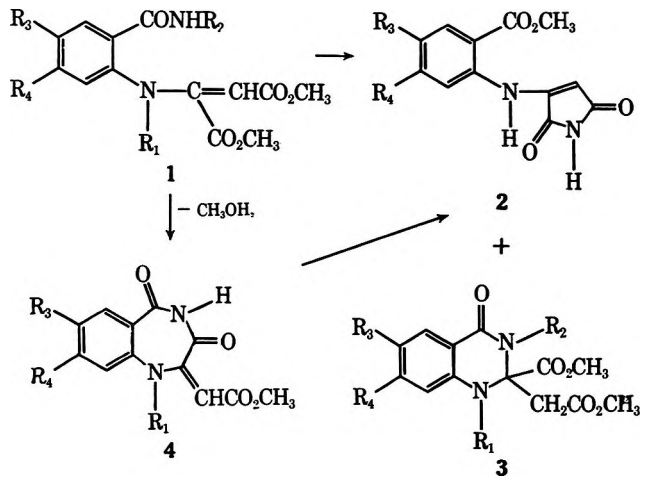
We have recently noted that enamines **1**, prepared by condensation of anthranilamides and dimethyl acetylenedicarboxylate, are versatile precursors of several classes of heterocyclics.[2] Treatment of **1** with NaOMe in xylene produces a new class of benzodiazepinediones **4**, which are labile in alcohol. The reaction of **1** with NaOMe in MeOH leads directly to maleimides **2** and quinazolinones **3**, which can also be obtained in the same ratio in a separate experiment as the ring contraction products of the benzodiazepinediones, thus pointing toward **4** as a possible intermediate.

The isolation of pure quinazolinones by this technique is tedious, since careful fractional separation from the maleimide coproducts is necessary, and only three quinazolinones (**3a–c**) were prepared by this route. With an *N*-methyl group on either the amide or amino nitrogen of the anthranilamide, steric hindrance apparently prevents formation of a benzodiazepinedione intermediate and only quinazolinone (**3d** or **3e**) (not admixed with maleimide) results in base-catalyzed cyclization of the corresponding adduct.

We have now found that the quinazolinones **3** can be obtained uncontaminated by benzodiazepine or maleimide coproducts, by simple thermolysis of the enamino adducts **1**. The quinazolinones obtained displayed two saturated ester carbonyls in their ir spectra between 1725 and 1750 cm^{-1} and a characteristic CH_2 resonance

(1) Department of Chemistry, Marshall University, Huntington, W. Va. 25701.

(2) N. D. Heindel, V. B. Fish, and T. F. Lemke, *J. Org. Chem.*, **33**, 3997 (1968).

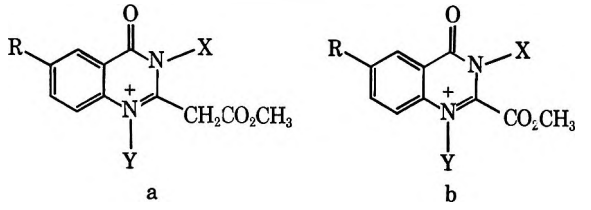


	R_1	R_2	R_3	R_4
a	H	H	H	H
b	H	H	Cl	H
c	H	CH_3	H	H
d	CH_3	H	H	H
e	CH_3	CH_3	H	H
f	H	C_6H_5	Cl	H
g	CH_3	H	Cl	H
h	H	CH_3	Cl	H
i	H	H	OCH_3	Cl
j	H	H	F	H

in the nmr at δ 3.18 ± 0.10 ppm. The mass spectral fragmentation patterns for several of the quinazolinones were tabulated (Table I) for the purpose of assigning fundamental pathways. Very few electron impact studies have been performed on this heterocyclic class.[3]

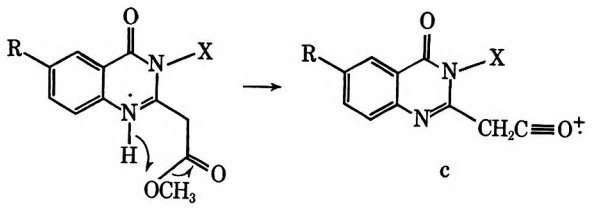
The molecular ions were observed for all the quinazolinones at very low abundancies (less than 0.1% of the base peak) except for the dimethyl compound **3e**, which has a parent ion of 2.7 relative intensity.

The nature of the substituents at C-2 in all the quinazolinones was clearly demonstrated by the appearance of the generally abundant ions, a and b, resulting from



a "type A_1" cleavage[4] of carbomethoxy ($\cdot CO_2Me$, 59 mass units) and carbomethoxymethyl ($\cdot CH_2CO_2Me$, 73 mass units), respectively, from the molecular ion.

Another general feature of the cracking patterns was the loss of methanol (mass 32) from the a species. The



(3) G. Spiteller, *Advan. Heterocycl. Chem.*, **7**, 343 (1966).

(4) K. Biemann, "Mass Spectrometry: Organic Chemical Applications," McGraw-Hill, New York, N. Y., 1962, pp 76–77.

TABLE I

MASS SPECTRA OF 2-CARBOMETHYL-2-CARBOMETHOXYMETHYL-3-R_1-2,3-DIHYDRO-6-R_2-4(*H*)-QUINAZOLINONES[a]

Compd	Molecular ion, *m/e*	*m/e* (rel abundance)
3a	278	219 (100), 205 (25), 187 (29), 173 (4.4), 160 (24), 159 (96), 146 (10), 145 (31), 132 (12), 130 (15), 129 (12), 120 (8.8), 119 (13), 91 (14), 90 (7.0), 89 (14)
3b	312	253 (14), 238 (75), 221 (1.0), 193 (7.6), 180 (100), 179 (27), 178 (32), 160 (12), 153 (50), 124 (42), 74 (35)
3c	292	233 (100), 219 (14), 201 (15), 173 (35), 159 (15), 146 (15), 132 (20), 104 (7.7)
3d	292	233 (100), 219 (23), 202 (7.9), 201 (49), 174 (8.8), 159 (8.8), 134 (10), 132 (7.9), 105 (16), 104 (16), 78 (10), 77 (18)
3e	306	306 (2.7), 248 (15), 247 (100), 233 (12), 215 (5.4), 188 (5.4), 160 (15), 145 (8.0), 114 (15), 73 (14)
3f	388	329 (53), 328 (100), 315 (14), 297 (21), 269 (57), 255 (9), 234 (8), 180 (8), 153 (9), 132 (54), 125 (7), 124 (10), 117 (10), 91 (9), 77 (40)
3g	326	326 (2.5), 267 (100), 253 (11), 235 (33), 208 (5.0), 193 (6.3), 168 (11), 166 (4.4), 139 (9.4), 138 (9.4), 111 (6.3), 77 (8.8), 75 (7.5)

[a] Values of ion abundancies (relative to base peak) of less than 1% and of ions containing the minor isotope of chlorine are omitted from the table.

process is envisioned as proceeding through a concerted, cyclic intermediate leading to species c.

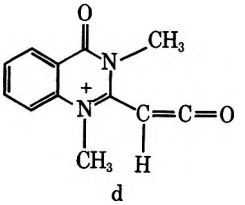
That the overall transition to these P − 91 ions did in fact encompass a distinct 32 mass loss was indicated by the presence of the appropriate metastable ions (Table II).

TABLE II

METASTABLE IONS

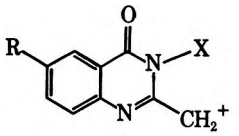
Compd	*m**	Transition	Calcd
3a	159.5	219 → 187	159.7
	135.4	187 → 159	135.2
	104.5	159 → 129	104.7
3b	130.0	180 → 152	130.1
3c	173.5	233 → 201	173.4
3d	173.5	233 → 201	173.4
3e	187.5	247 → 215	187.1
3g	207	267 → 235	206.8

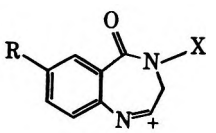
This same pathway was not available to the dimethyl derivative **3e**, and thus an alternative route to the *m/e* 215 ion appears to be the loss of methanol totally from the side chain, leading to species d.



The P − 91 species (c or d) further fragmented with losses of either CO (mass 28) or ketene (mass 42). The product of the first loss is the result of losing the side

chain carbonyl function to form e or its ring-expanded version f.

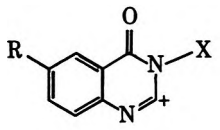

e

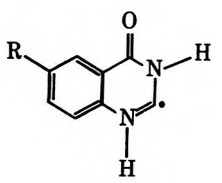

f

This transition was verified by the occurrence of a metastable peak for **3a** at 135.4 (Table II). This process did not occur for any of the quinazolinones with a methyl group at N-1.

Support for the intermediacy of a ring-expanded species was evidenced in at least one case by the facile loss of CH_2NH_2 (mass 30) from **3a** (metastable ion at 104.5), plausible only for species f.

Formation of ion g was observed for all the quinazolinones. This ion could arise by a McLafferty rearrangement of a or by loss of ketene from c.

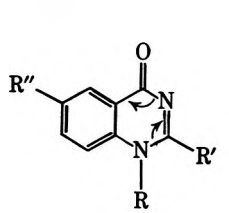
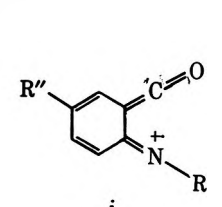

g


h

In the cases of **3a,b** this species could also have arisen from the loss of a hydrogen from h, which was produced by consecutive losses of $\cdot CO_2Me$ and $\cdot CH_2CO_2Me$ from the molecular ion.

Other prominent features of the high-mass portion of the spectra were the large abundances of the *m/e* 238 ion for **3b** and the *m/e* 328 ion for **3f** arising from McLafferty rearrangements with concomitant losses of CH_3CO_2Me and HCO_2Me, respectively, from the molecular ions.

Some of the compounds showed a tendency to undergo a retro Diels–Alder cleavage (type D)[5] in the same manner reported by Budzikiewicz, *et al.*,[6] for a series of quinazolinones in which the preferred cleavage of atoms 2 and 3 led to species i.



i

Important fragmentations of this type were observed for **3a** and **3f**, leading to ions *m/e* 119 (p − 159) and 153 (p − 236), respectively.

The contribution of this fragmentation pattern (**3b**) (*m/e* 153, p − 159) was uncertain due to the ease at which another process occurred, verified by the presence of a metastable ion at *m/e* 130 and due to the loss of HCN (mass 27) from the base peak.

(5) F. W. McLafferty, "Mass Spectrometry of Organic Ions," Academic Press, New York, N. Y., 1963, p 423.

(6) S. C. Pakrashi, J. Bhattacharyya, L. F. Johnson, and H. Budzikiewicz, *Tetrahedron*, **19**, 1011 (1963).

Experimental Section

Melting points were determined between glass slide covers on a Fisher-Johns block and are reported uncorrected. Nmr spectra were determined on a Varian A-60 spectrometer using TMS as an internal standard.

Mass spectra were run on a Hitachi Perkin-Elmer RMU-6E high-resolution instrument equipped with a double-focusing sector and a direct solids inlet system. All of the compounds were analyzed by placing approximately 1 mg of the sample into a 1-mm i.d. quartz tube which was introduced into the ion source of the spectrometer by a vacuum interlock. It was necessary to elevate the temperature of the direct inlet system to 80° in order to achieve ionization at 80 eV. At this temperature, a quite singular mass spectrum was obtained for each of the compounds. High mass calibration of the spectra was accomplished by the use of tungsten hexacarbonyl as an internal standard.

Microanalyses were performed by the late Dr. V. B. Fish of these laboratories and by Dr. G. I. Robertson of Florham Park, N. J.

Anthranilamides.—These materials, with exceptions as noted, were prepared by nucleophilic ring opening of isatoic anhydrides with amines and have been described in the literature.[2,7,8]

Preparation of Dimethyl Acetylenedicarboxylate Adducts of Anthranilamides.—Reaction of equimolar amounts of the anthranilamide and dimethyl acetylenedicarboxylate in refluxing MeOH (0.1 mol/100 ml of solvent) produced the desired adducts. This procedure has been previously described for **1a–c**[2] and for **1i–j**[8] and was applied herein to the preparation of **1d–h**. The adduct **1e**, prepared from 2-(*N*-methylamino)-*N*-methyl benzamide, was a viscous oil and was utilized directly in synthesis of the quinazolinone.

1d was prepared in 71% yield by reaction of 2-(*N*-methylamino)benzamide and dimethyl acetylenedicarboxylate. Light yellow crystals, mp 161.5–163° (from benzene), were obtained.

Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.52; H, 5.51; N, 9.58. Found: C, 57.81; H, 5.77; N, 9.74.

1f, prepared by condensation of 2-amino-5-chlorobenzanilide and the alkyne ester, was obtained in 71% yield, mp 143–145° (from MeOH).

Anal. Calcd for $C_{19}H_{17}ClN_2O_5$: C, 58.69; H, 4.41; N, 7.20. Found: C, 58.65; H, 4.21; N, 7.40.

1g was obtained by reaction of 2-(*N*-methylamino)-5-chlorobenzamide with dimethyl acetylenedicarboxylate in 80% yield. The analytical sample, mp 171.5–172.5°, was isolated by recrystallization from MeOH.

Anal. Calcd for $C_{14}H_{15}ClN_2O_5$: C, 51.46; H, 4.63; N, 8.57. Found: C, 51.72; H, 4.48; N, 8.43.

1h, prepared in 75% yield by condensation of 2-amino-5-chloro-*N*-methylbenzamide and dimethyl acetylenedicarboxylate, melted at 163–165° after two recrystallizations from MeOH.

Anal. Calcd for $C_{14}H_{15}ClN_2O_5$: C, 51.46; H, 4.63; N, 8.57. Found: C, 51.51; H, 4.60; N, 8.28.

1e was obtained as a viscous oil by condensation of 2-(*N*-methylamino)-*N*-methylbenzamide[9] with acetylenedicarboxylate by the previously described method.[2,8] This oil was converted to the quinazolinone **3e** by redissolving in MeOH containing 0.1 g of NaOMe, then refluxing for 24 hr, concentrating, and diluting with water. The crude product precipitate (63%) was recrystallized from 95:5 cyclohexane–benzene to yield the analytical material, mp 85–86.5°.

Anal. Calcd for $C_{15}H_{18}N_2O_5$: C, 58.82; H, 5.92; N, 9.15. Found: C, 58.72; H, 5.81; N, 9.24.

Thermal Cyclizations to Quinazolinones.—The other quinazolinones reported herein were prepared by fusion of the anthranilamide adducts at 15–30° above their melting points. A sample procedure, illustrated by the synthesis of **3f**, follows.

6-Chloro-2-carbomethoxy-2-carbomethoxymethyl-2,3-dihydro-3-phenyl-4-(1*H*)-quinazolinone (3f).—A 1.94-g (5.0 mmol) sample of **1f** was heated in an open tube at 165–175° for 2 hr. The cooled residue was then triturated with a mixture of equal parts of benzene and cyclohexane and filtered. The collected crystals (1.53 g, 79%) were washed with cyclohexane and re-

(7) N. D. Heindel, W. P. Fives, T. F. Lemke, and R. A. Carrano, *J. Pharm. Sci.*, **60**, 703 (1971).

(8) N. D. Heindel, W. P. Fives, T. F. Lemke, J. E. Rowe, H. W. Snady, and R. A. Carrano, *J. Med. Chem.*, **14**, 1233 (1971).

(9) H. Yale, *J. Heterocycl. Chem.*, **8**, 193 (1971).

crystallized from methanol to yield the pure quinazolinone **3f**: mp 198–200°; ir (Nujol mull) 3260 (NH), 1752 and 1738 (ester CO), and 1638 cm^{-1} (amide CO); nmr (DMSO-d_6) δ 7.93 (s, 1, NH, exchanges with D_2O), 7.58–7.26 (m, 7, ArH), 6.85 (d, 1, J_o = 8.5 Hz, ArH_8), 3.64 (s, 3, OCH_3), 3.19 (s, 3, OCH_3), and 3.13 ppm (s, 2, CH_2CO).

Anal. Calcd for $C_{19}H_{17}ClN_2O_5$: C, 58.69; H, 4.41; N, 7.20. Found: C, 58.94; H, 4.20; N, 7.19.

2-Carbomethoxy-2-carbomethoxymethyl-6-chloro-2,3-dihydro-1-methyl-4(1*H*)-quinazolinone (3g).—Pyrolysis of 1g provided an 88% yield of **3g**, which was recrystallized from benzene, mp 180–182°.

Anal. Calcd for $C_{14}H_{15}ClN_2O_5$: C, 51.46; H, 4.63; N, 8.57. Found: C, 51.64; H, 4.55; N, 8.67.

2-Carbomethoxy-2-carbomethoxymethyl-6-chloro-2,3-dihydro-3-methyl-4(1*H*)-quinazolinone (3h).—A 94% yield of **3h** was obtained from **1h**. Recrystallization from 1:1:1 MeOH–benzene–cyclohexane provided the analytical sample, mp 147.5–149°.

Anal. Calcd for $C_{14}H_{15}ClN_2O_5$: C, 51.46; H, 4.62; N, 8.57. Found: C, 51.53; H, 4.47; N, 8.67.

2-Carbomethoxy-2-carbomethoxymethyl-6-methoxy-7-chloro-2,3-dihydro-4(1*H*)-quinazolinone (3i).—**3i** was obtained by pyrolysis of 1i. Four recrystallizations from MeOH gave the purified product (36%),[10] mp 169.5–171.5°.

Anal. Calcd for $C_{14}H_{15}ClN_2O_6$: C, 49.06; H, 4.41; N, 8.17. Found: C, 49.36; H, 4.58; N, 8.07.

2-Carbomethoxy-2-carbomethoxymethyl-6-fluoro-2,3-dihydro-4(1*H*)-quinazolinone (3j).—This compound was prepared in 36%[10] yield from **1j**, mp 178–180° (after recrystallization from MeOH).

Anal. Calcd for $C_{13}H_{13}FN_2O_5$: C, 52.70; H, 4.42; N, 9.45. Found: C, 52.92; H, 4.48; N, 9.42.

2-Carbomethoxy-2-carbomethoxymethyl-2,3-dihydro-1-methyl-4(1*H*)-quinazolinone (3d).—**3d** was prepared by dissolving 3.0 g (0.01 mol) of **1d** in 50 ml of xylene containing 0.1 g of NaOMe and heating to reflux for 3.5 hr. Chilling precipitated 1.32 g of unreacted **1d**. Dilution of the filtrate with petroleum ether (bp 30–60°) gave 1.18 g of product. Two recrystallizations from MeOH yielded 1.02 g (34% conversion) of pure **3d**,[10] mp 118–120°.

Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.52; H, 5.51; N, 9.58. Found: C, 57.73; H, 5.41; N, 9.53.

Registry No.—**1d**, 34804-41-6; **1e**, 34804-42-7; **1f**, 34804-43-8; **1g**, 34804-44-9; **1h**, 34804-45-0; **3a**, 17244-35-8; **3b**, 17244-36-9; **3c**, 17244-40-5; **3d**, 34804-49-4; **3e**, 34804-50-7; **3f**, 34804-51-8; **3g**, 34803-90-2; **3h**, 34803-91-3; **3i**, 34803-92-4; **3j**, 34803-93-5.

Acknowledgment.—We gratefully acknowledge the financial support of the doctoral research of Thomas F. Lemke by Atlas Chemical Industries.

(10) The low yields of these compounds are partially a result of the increased solubility in the recrystallization solvents. No attempt was made to optimize the yields.

Synthesis of Trimethylhydroquinone from Aliphatic Precursors

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Received January 25, 1972

Condensation of a properly substituted α,β-unsaturated aldehyde or ketone with an appropriate aliphatic ketone leads to a trimethyl-2-cyclohexen-1-one structure. These molecules are readily aromatized to the corresponding phenols in high purity with Pd/C under mild conditions. A novel indirect electrolytic oxidation involving Fremy's radical[2] yielded trimethyl-*p*-benzoquinone (**9**) which in turn was reduced to trimethylhydroquinone (**1**). The latter is an important intermediate in the synthesis of vitamin E.

Various methyl-substituted phenols and particularly trimethylphenols are prepared from phenol *via* methylation processes. Although these processes can be controlled so that a particular mono- or polymethylated phenol can be obtained as the major product, mixtures are invariably obtained. Such mixtures require separation by methods which can be tedious especially if phenols of high purity are required.

We now wish to describe a general method for obtaining a number of specifically substituted trimethylphenols in pure form. Since only standard laboratory techniques are involved, the overall scheme should lend itself to the preparation of a variety of ^{14}C ring- and/or chain-labeled phenols, *p*-quinones, and the hydroquinones derived thereform.

Our main objective was to find a practical synthesis for 2,3,5- and/or 2,3,6-trimethylphenol based on readily available aliphatic starting materials. Both of these phenols represent important intermediates in the production of trimethylhydroquinone and thus of vitamin E.

The basic concept comprised the construction of a suitably substituted trimethylcyclohexenone carbon skeleton which, in a second step, could be aromatized to the corresponding trimethylphenol (Scheme I).[3]

Chapurlat and Dreux[4] described the condensation of 3-penten-2-one with 2-butanone to yield 3,5,6-trimethyl-2-cyclohexen-1-one (**2**). We found that the same product was obtained from the more readily accessible 4-chloro-2-pentanone[5] and 2-butanone. A different substitution pattern was obtained in the cyclohexenone ring when methyl vinyl ketone was condensed with 3-pentanone under strongly alkaline conditions. The uv absorption at λ_{max}^{EtOH} 239 nm was compatible with the 2,3,6-trimethyl-2-cyclohexen-1-one[6] structure, **4**.

The reaction we studied most carefully was the condensation of crotonaldehyde with 3-pentanone in the presence of KOH.[7] Under optimal conditions a 77% yield (uv analysis) of **6** as a mixture of cis and trans isomers (nmr) was obtained.

(1) To whom correspondence should be addressed.

(2) P. A. Wehrli and F. Pigott, *Inorg. Chem.*, **9**, 2614 (1970).

(3) No stereochemistry is indicated in **2**, **6**, and **7**.

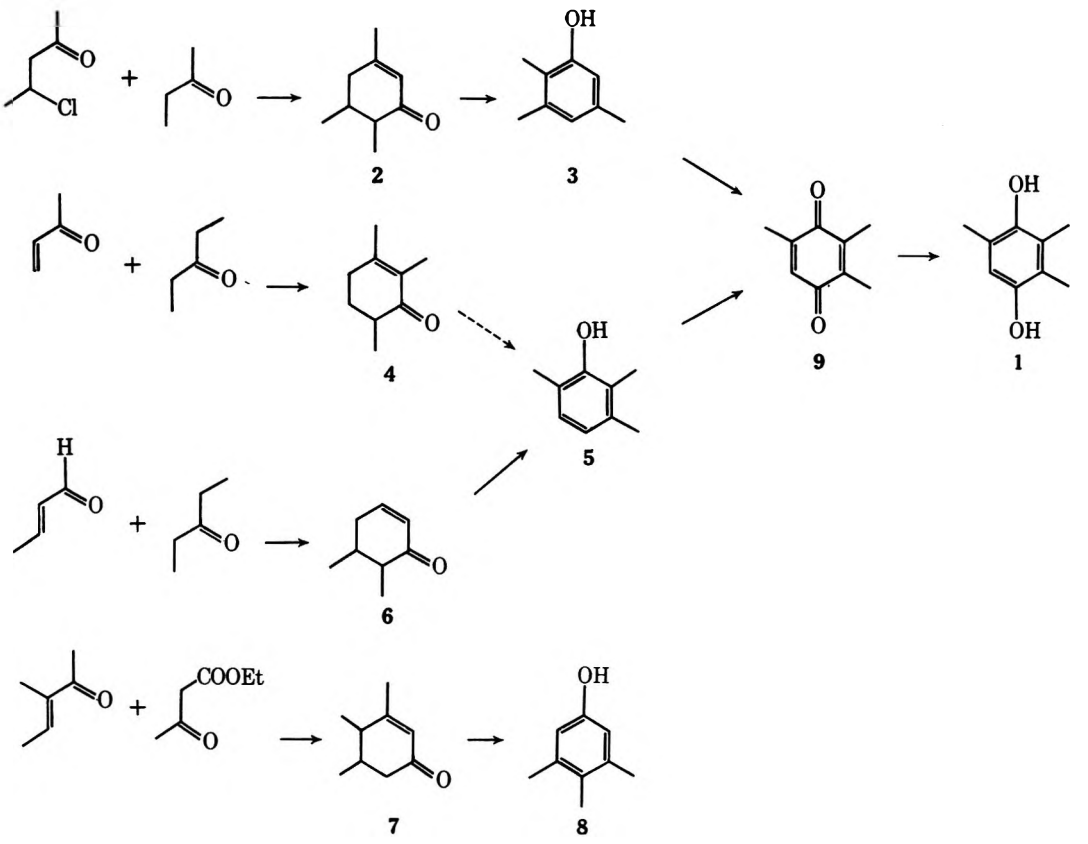
(4) R. Chapurlat and J. Dreux, *C. R. Acad. Sci.*, **253**, 2361 (1961): bp for **2**, 85–86° (4.5 mm).

(5) A. Wohl and R. Maag, *Chem. Ber.*, **43**, 3280 (1910); 4-chloro-2-pentanone is undoubtedly an intermediate in their preparation of 3-penten-2-one.

(6) T. Ichikawa, H. Owatari, and T. Kato, *Bull. Chem. Soc. Jap.*, **41**, 1228 (1968): bp for **4**, 92–96° (16 mm); bp for **6**, 92–100° (24 mm).

(7) After this work was completed, we became aware of a Dutch Patent abstract (6,903,484, Sept 10, 1969): bp for **6**, 74–76° (12 mm).

SCHEME I



The condensation of 3-methyl-3-penten-2-one with ethyl acetoacetate took the expected course with the formation of the hitherto unknown 3,4,5-trimethyl-2-cyclohexen-1-one (**7**). Structure **7** was confirmed by transformation to phenol **8**.

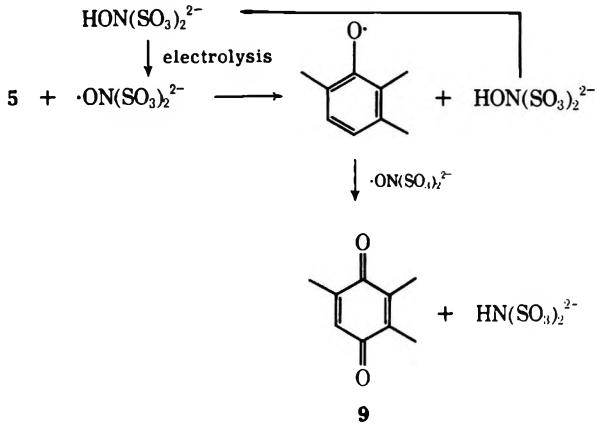
Surprisingly smooth aromatizations of cyclohexenones **2**, **6**, and **7** were achieved by refluxing the compounds in the presence of palladium on charcoal. Only the conversion **6** → **5** was studied in detail. The resulting trimethylphenols were identified with authentic samples by comparison.

Phenols **3** and **5** were converted to the same trimethyl-*p*-benzoquinone **9** by application of a novel indirect electrolytic oxidation. Thus, an aqueous solution of hydroxylamine disulfonate was electrolyzed[2] in the presence of a heptane solution of **3** or **5** to give the *p*-quinone in quantitative yield from **5** and in somewhat lower yield from **3**. Use of the two-phase system protects the *p*-quinone from undergoing side reactions. Furthermore, by carrying out the preparation of Fremy's radical in the presence of the phenol, only 1 mol of hydroxylamine disulfonate is required to achieve the overall oxidation of a phenol to a quinone (Scheme II).[8]

As indicated in Scheme II, the first step in the Teuber reaction[9] is catalytic with respect to Fremy's radical under electrolysis conditions. A molar quantity of the reagent, however, is consumed in the second step.

Reduction of *p*-quinone **9** by standard methods gave the desired trimethylhydroquinone **1** in a high state of purity.

SCHEME II



Experimental Section[10]

3,5,6-Trimethyl-2-cyclohexen-1-one (**2**).—4-Chloro-2-pentanone (30 g, 0.25 mol) and 108 g (1.5 mol) of 2-butanone were stirred at room temperature and 20 g (0.25 mol) of pyridine was added over a period of 2 min. The temperature rose from 25° to 34°. The reaction mixture was stirred at room temperature for 15 min and then a small amount of a heavy liquid phase which had precipitated was removed with a pipette; 5 *M* sodium methoxide (100 ml, 0.5 mol) in methanol was added. The temperature rose to 52° and the reaction mixture was refluxed for 1 hr, cooled, and filtered from 11.5 g of sodium chloride. It was then partitioned between ether and saturated sodium chloride solution. The ether phase was washed once with dilute hydrochloric acid, followed by three washes with saturated

(8) H. J. Teuber and W. Rau, *Chem. Ber.*, **86**, 1036 (1953).
(9) H. J. Teuber and K. H. Dietz, *Angew. Chem.*, **77**, 913 (1965).

(10) Infrared and uv spectra were recorded on a Perkin-Elmer Model 21 and on a Cary Model 14 spectrophotometer respectively. Nmr spectra were carried out on a Varian A-60 apparatus and are reported in parts per million. Melting points were determined in capillaries on a Thomas-Hoover apparatus and are not corrected. The equipment used for the electrolytic oxidation is described in ref 2.

sodium chloride solution (until the aqueous wash was no longer acidic to pH paper). The ether phase was dried over anhydrous sodium sulfate and concentrated *in vacuo*. Distillation of the residue gave 10.0 g (29%) of a slightly yellow liquid boiling at 93–106° (18–19 mm). The analytical sample distilled at 106–107° (18 mm): ir ($CHCl_3$) 1670 (s), 1390 cm^{-1} (m); $\lambda_{max}^{i\text{-PrOH}}$ 233 nm (ϵ 14,000); nmr ($CDCl_3$) δ 1.0–1.35 (m, 6 H), 2.0–2.7 (m, 7 H), 6.0 (s, broad, 1 H), spectrum indicates mixture of diastereoisomers.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 77.98; H, 10.21.

2,3,6-Trimethyl-2-cyclohexen-1-one (4).—To a solution of 34.4 g (0.4 mol) of 3-pentanone and 10 ml of methanol was added 12 g (0.1 mol) of potassium *tert*-butoxide. The temperature rose to 34°. With a dropping funnel there was added slowly 14.0 g (0.2 mol) of methyl vinyl ketone with vigorous stirring. The temperature rose to 50°. The reaction was stirred for 10 min longer. The dark brown mixture was partitioned between ether and saturated sodium chloride solution. The organic phase was washed with saturated sodium chloride solution until neutral. After drying over anhydrous sodium sulfate, evaporation of the solvent, and distillation of the residue there was obtained a fraction weighing 1.5 g and boiling at 93–95° (19 mm). A redistilled sample was characterized: ir ($CHCl_3$) 1660 (s) and 1640 cm^{-1} (s); $\lambda_{max}^{i\text{-PrOH}}$ 239 nm (ϵ 12,100); nmr ($CDCl_3$) δ 1.15 (d, 3 H), 1.7 (s, broad, 3 H), 1.9 (s, broad, 3 H), 2.0–2.6 (m, 5 H); mass spectrum M^+ *m/e* 138, base peak at *m/e* 96.

2,5,6-Trimethyl-2-cyclohexen-1-one (6).—A 1.2-l., three-necked flat-bottomed flask, equipped with a mechanical paddle stirrer, thermometer, and addition funnel with the glass delivery tube pulled out at the end, was charged with 64.5 g (1 mol) of 85% potassium hydroxide pellets and 75 g of methanol. The mixture was stirred until the potassium hydroxide was largely dissolved. To the warm mixture was added 430 g (5 mol) of 3-pentanone and the mixture was stirred for a few minutes at 40°. With vigorous stirring so that there was a very deep whirlpool effect, 70.0 g (1 mol) of crotonaldehyde was added dropwise at a rate so the addition would be complete in *ca.* 40 min. After the rate was set (judged visually) the delivery tip was submerged into the swirling reaction mixture so that the addition took place below the surface, thus ensuring most rapid distribution of the crotonaldehyde. The temperature was maintained at 40–45° throughout the addition. The reaction mixture turned dark and the potassium hydroxide pellets were completely dissolved on completion of the addition of the crotonaldehyde. The mixture was stirred for 10 min, cooled in an ice bath, and acidified with concentrated hydrochloric acid while cold. The point of neutralization was readily recognized when the color of the reaction mixture changed from dark brown to light yellow at slightly acidic pH. After extracting three times with diethyl ketone, washing the organic layer with saturated sodium chloride solution, and evaporating the solvent on a rotary evaporator, there remained a clear golden liquid residue weighing 167 g (yield, estimated by uv, 77%). Distillation *in vacuo* through a 30-mm Vigreux column yielded a colorless main fraction, 97 g, bp 74–81° (12 mm)[6,7] (70% based on crotonaldehyde). An analogously prepared sample was analyzed: ir ($CHCl_3$) 1655 cm^{-1} (s); $\lambda_{max}^{i\text{-PrOH}}$ 232 nm (ϵ 8980); nmr ($CDCl_3$) δ 0.95–1.12 (m, 6 H), 1.75 (s, broad, 3 H), 1.8–2.5 (m, 4 H), 6.62 (broad, 1 H); mass spectrum M^+ 138, base peak at *m/e* 82.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 77.92; H, 10.19.

3,4,5-Trimethyl-2-cyclohexen-1-one (7).—Ethyl acetoacetate (13.0 g, 0.1 mol), 3-methyl-3-penten-2-one (9.8 g, 0.1 mol), and a 25% solution of sodium methoxide in methanol (22 ml, 0.1 mol) were refluxed for 18 hr. Precipitation occurred within 1 hr and there was a considerable amount of bumping. The reaction mixture was cooled, treated with water and concentrated hydrochloric acid (gas evolution occurred), and extracted with ether. The ether layer was dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford 15.0 g of residue, $\lambda_{max}^{i\text{-PrOH}}$ 233 nm. The residue was treated with 75 ml of a 10% sodium hydroxide solution and stirred for 5 hr to ensure complete saponification and decarboxylation. It was then extracted with ether and concentrated to afford 10.0 g of a residue. Distillation at 18–20 mm gave 6.4 g (46.5%) of product boiling at 107–111°.

Combined material from two similar reactions was redistilled, bp 109–110° (1.8 mm) (colorless oil) for analysis: ir ($CHCl_3$) 1663 cm^{-1} (s); $\lambda_{max}^{i\text{-PrOH}}$ 233 nm (ϵ 14,480); nmr ($CDCl_3$) δ 0.93–1.33 (m, 6 H), 1.96–2.16 (m, 3 H), 2.16–2.46 (m, 4 H), 5.9–6.03 (s, 1 H); mass spectrum M^+ at *m/e* 138 (fragmentation compatible).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.20; H, 9.96.

2,3,5-Trimethylphenol (3).—3,5,6-Trimethyl-2-cyclohexen-1-one (2) (1.0 g) was refluxed vigorously and stirred with 100 mg of 10% palladium on charcoal. After *ca.* 4 hr, the evolution of hydrogen stopped. Reflux was continued for 6 hr. The reaction mixture was cooled, diluted with 2 ml of heptane, and filtered through a medium sintered glass funnel. After washing thoroughly with hot heptane, the filtrate was evaporated to *ca.* 5 ml and cooled for 18 hr at 0°. The crystals were filtered, washed with heptane, and air dried to give 500 mg (50%) of 2,3,5-trimethylphenol, mp 90.1–91.1°. The ir spectrum of this material was superimposable with that of an authentic sample.[11]

2,3,6-Trimethylphenol (5).—2,5,6-Trimethyl-2-cyclohexen-1-one (6) (138 g, 1.0 mol) was weighed into a 1-l. three-necked flask and 7.0 g of 10% palladium on charcoal was added. The flask was equipped with a heating mantle, magnetic stirrer, thermometer, and an efficient water-cooled condenser. The top of the condenser was connected by Tygon tubing to a cooling trap (Dry Ice–acetone) and from there to another 1-l. three-necked flask (safety container), the outlet of which led to a gas measuring device. Before heating, the whole apparatus was flushed carefully with nitrogen. At the onset of reflux collection of hydrogen was started. The first liter was produced very rapidly (*ca.* 5 min). Then a marked slowdown in the evolution of hydrogen occurred for about 30 min. At the end of this induction period, hydrogen started to come off at increasing speeds. The maximum observed under these conditions was 1 l. in 15 min. While very vigorous reflux was maintained throughout the reaction, the evolution of hydrogen generally stopped after 7 to 8 hr, by which time 17–18 l. of hydrogen had been collected in the measuring device. The contents of the flask were cooled to about 100° and flushed with a slow stream of nitrogen. Heptane (100 ml) was introduced through the condenser and the still hot reaction mixture was filtered over a medium sintered glass funnel. Equipment and charcoal were washed with three 50-ml portions of hot heptane. Vpc analysis of the filtrate indicated a 2,3,6-trimethylphenol content of 92–93% on an area comparison (100°, isothermal, 2% silicone–rubber, 1 in. per minute). The colorless filtrate was crystallized for 18 hr at 0°. It was then filtered and washed with three 25-ml portions of cold heptane. After air drying for 4 hr, at room temperature, there resulted a crop of 98.3 g (72%) of pure 5 with a melting point of 63.5–64° (Mettler automatic melting point apparatus).[12]

The mother liquor was extracted directly with six 25-ml portions of 4 *N* sodium hydroxide and the individual portions were combined and acidified with concentrated hydrochloric acid with cooling. Extraction with heptane at *ca.* 40° followed by drying the organic layers over magnesium sulfate and evaporation afforded a solidified residue of 21 g (total yield, 88%). The melting point of this material was 60°.

3,4,5-Trimethylphenol (8).—3,4,5-Trimethyl-2-cyclohexen-1-one (7) (1 g) and 5% palladium on charcoal (0.1 g) were heated and stirred at 180–190°. After 10 min the foaming had ceased. Heating was continued for a total of 1.75 hr, when the uv spectrum showed it to be a mixture of phenol and starting material. Heating was continued for 1 hr longer at 208–218°. At the end of this time, it was cooled, diluted with ether, filtered, and concentrated on the steam bath. The residue was treated with 40% sodium hydroxide solution and the resulting precipitate was filtered and redissolved in fresh water. The aqueous phase was washed with ether and acidified with 6 *N* hydrochloric acid. An oil precipitated which solidified on standing. It was collected and air dried, yield 170 mg. The ir spectrum of this material was superimposable with that of an authentic sample of 3,4,5-trimethylphenol.

Trimethyl-*p*-benzoquinone (9). **A. From 2,3,6-Trimethylphenol (5).**—In the following sequence, 15.0 g (0.217 mol) of sodium nitrite, 250 g of ice, and 41.6 g (0.4 mol) of sodium bisulfite were weighed into an ice-cooled 1-l. resin flask. With manual stirring, 22.5 ml (23.6 g, 0.4 mol) of acetic acid was added. Most of the ice dissolved and the temperature dropped to −3°. The clear solution was kept at this temperature and stirred mechan-

(11) Obtained from Aldrich Chemical Co.

(12) W. C. Sears and L. J. Kitchen, *J. Amer. Chem. Soc.*, **71**, 4110 (1949), report mp 61.8–62.8°.

ically for 1.5 hr. At the end of this period 250 ml of a saturated solution of sodium carbonate was added. To this resulting solution of sodium hydroxylamine disulfonate 20.0 g (0.147 mol) of 2,3,6-trimethylphenol (mp 63.4°) and 100 ml of heptane were added. A stainless steel anode[10] (*ca.* 10 mesh/cm²) was immersed into the heterogeneous two-phase system. The cathode, in the form of a stainless steel coil, was placed into a porous pot (Soxhlet type extraction thimble), filled with water plus 2 ml of the electrolyte, and immersed to about ¾ of its length into the two-phase reaction mixture. The cold two-phase system was now stirred mechanically and electrolyzed for 5 hr at 7–8V/3A at 0–5°. The trimethylphenol dissolved slowly and the color of the hexane layer changed to yellow, then to orange, and again to lemon yellow at the end. The course of the reaction was conveniently followed by tlc (aluminum oxide plates, chloroform, phosphomolybdic acid spray). Only trace amounts of phenol could be detected at the end of the electrolysis. The water layer had a violet color and some inorganic material crystallized. The whole mixture was transferred into a 1-l. separatory funnel. The yellow heptane layer was separated and washed two times with 50 ml of 4 *N* sodium hydroxide and then with saturated sodium chloride solution until the washes were neutral. The water layers were washed twice with heptane. The heptane extracts were combined, dried over magnesium sulfate, filtered, and evaporated to dryness (rotary evaporator, 40° bath temperature). The residue, a lemon oil, crystallized under cold running water. The last traces of solvent were subsequently removed under high vacuum. This procedure gave 20.8 g (94%) of crystalline, yellow trimethylbenzoquinone (**9**), mp 29.6–31°[13] (Mettler automatic melting point apparatus) and tlc examination of this material revealed only one spot.

B. From 2,3,5-Trimethylphenol (3).—Using the same procedure described in A, **9** was obtained in 73% yield, mp 27.8°.

Trimethylhydroquinone (1).—Reduction of a sample of **9** with sodium hydrosulfite and crystallization from water yielded pure **1**, mp 170–173°.[13] Ir and uv spectra of this material were superimposable with those of an authentic sample.[11]

Registry No.—**1**, 700-13-0; **2**, 16782-79-9; **3**, 697-82-5; **4**, 20030-29-9; **5**, 2416-94-6; **6**, 20030-30-2; **7**, 34638-67-0; **9**, 935-92-2.

Acknowledgments.—Thanks are due to the staff of our Physical Chemistry Department directed by Dr. P. Bommer. In particular we are indebted to Dr. H. Wyss for ir, Dr. V. Toome for uv, Dr. T. Williams for nmr, Dr. W. Benz for mass spectra, and Dr. F. Scheidl for microanalyses.

(13) R. Nietzki and J. Schneider, *Chem. Ber.*, **27**, 1426 (1894), report mp 32° for **9** and 169° for **1**.

Notes

On the Electrophilic Substitutions and Additions to the Pyrrolidine Enamine of 1-Acetyl-3-oxopiperidine

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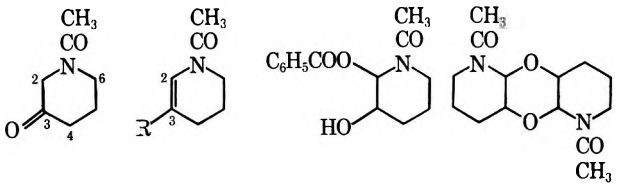
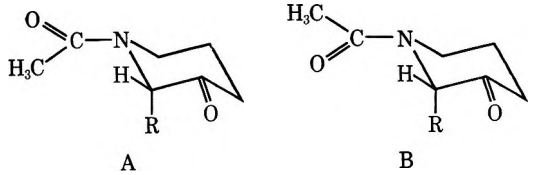
Enamine chemistry has been investigated extensively[1] since Stork's excellent application of enamines for electrophilic substitution reactions.[2] However, only a few examples have been reported of substitutions or additions to enamines of ketones bearing a methylene group flanked by a carbonyl group and a nitrogen atom.[3] In connection with research on synthesis of veratramine,[4] we have examined some reactions of the pyrrolidine enamine of 1-acetyl-3-oxopiperidine (**1**).

The starting ketone **1** was prepared as follows. Treatment of 1-acetyl-1,4,5,6-tetrahydropyridine[5] (**2**) with perbenzoic acid afforded the hydroxy derivative **3** in 50% yield, which on pyrolysis produced **1** in 72% yield along with a dimeric by-product **4**. In accordance with the structure, compound **1** exhibited a peak at *m/e* 141 (M^+) and absorption maxima at 1726 and 1642 cm^{-1} in the mass and ir spectra, respectively. The nmr spectrum of **1** was simplified by rapid ring inversion and, conversely, complicated by the presence of two conformers A and B (R = H) caused by slow rotation of the acetyl group around the C–N bond,[6] as



1 **2**, R = H **3** **4**

5, R = NC_4H_8



A B

(1) For recent reviews, see (a) G. H. Alt in "Enamines," A. G. Cook, Ed., Marcel Dekker, New York, N. Y., 1969, p 115; (b) K. Bláha and O. Červinka in "Advances in Heterocyclic Chemistry," Vol. 6, A. R. Katritzky and A. J. Boulton, Ed., Academic Press, New York, N. Y., 1966, p 147; (c) J. Szmuszkovicz in "Advances in Organic Chemistry," Vol. 4, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience, New York, N. Y., 1963, p 1.

(2) G. Stork, R. Terrel, and J. Szmuszkovica, *J. Amer. Chem. Soc.*, **76**, 2029 (1954); G. Stork and H. K. Landesman, *ibid.*, **78**, 5128, 5129 (1956).

(3) *E.g.*, S. Danishefsky and R. Cavanaugh, *J. Org. Chem.*, **33**, 2959 (1968).

(4) (a) T. Masamune, M. Takasugi, A. Murai, and K. Kobayashi, *J. Amer. Chem. Soc.*, **89**, 4521 (1967); (b) T. Masamune, M. Takasugi, and A. Murai, *Tetrahedron*, **27**, 3369 (1971).

(5) C. Schöpf, A. Komzak, F. Braun, and E. Jacobi, *Justus Liebigs Ann. Chem.*, **559**, 1 (1948); T. Masamune and M. Takasugi, *Yuki Kagobutsu Goseiho*, **18**, 1 (1968).

(6) For recent papers concerning the slow rotation of the C–N bond, see W. E. Stewart and T. H. Siddal, *Chem. Rev.*, **70**, 517 (1970); B. U. Schlottmann, *Tetrahedron Lett.*, 1221 (1971); C. R. Narayanan and B. M. Sawant, *ibid.*, 1321 (1971).

TABLE I

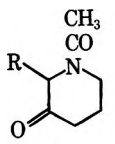
RESULTS IN ALKYLATIONS OF PYRROLIDINE ENAMINE OF 1-ACETYL-3-OXOPIPERIDINE (1)

Run	Alkylating reagents	Products	R in 6	Yield,[a,b] %
a	Benzyl chloride	6a	Benzyl	44 (53)
b	1-Phenylethyl bromide[c]	7b	1-Phenylethyl	33
		8b	1-Phenylethyl	20
c	1-(*o*-Tolyl)ethyl bromide[d]	7c	1-(*o*-Tolyl)ethyl	27
		8c	1-(*o*-Tolyl)ethyl	17
d	Allyl bromide	6d	Allyl	62 (67)
e	*n*-Butyl iodide	6e	*n*-Butyl	13 (57)
f	Phenacyl bromide	6f	Phenacyl	76 (55)
g	Bromoacetone	6g	2-Oxopropyl	40 (40)
h	Ethyl bromoacetate	6h	Ethoxycarbonylmethyl	40 (58)
i	Chloromethyl methyl ether	6i	Methoxymethyl	6 (33)
j	Ethyl acrylate	6j	2-Ethoxycarbonylethyl	48 (80)
k	Acrylonitrile	6k	2-Cyanoethyl	52 (80)

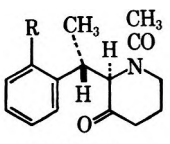
[a] Yields of isolated products. [b] The numbers in parentheses denote yields of the corresponding reactions to cyclohexanone under comparable conditions, and are cited from ref 1c. [c] H. Rupe and W. Tomi, *Chem. Ber.*, 47, 3064 (1914). [d] See footnote 9.

revealed by *two* sharp singlets (τ 7.89 and 7.82, NCO-CH_3), *two* overlapped triplets (B, τ 6.35 and 6.29, H at C_6), and *two* singlets (A, τ, 5.97 and 5.83, H at C_2). In fact, signals A and B remained unchanged on irradiation at τ 7.52 (H at C_4), while the latter B was simplified to two singlets by irradiation at τ 7.95 (H at C_5). The by-product was assigned formula **4** on the basis of the mass (*m/e* 282, M^+) and ir spectra (ν_{max} 1650 cm^{-1} and no absorption near 3300 and 1720 cm^{-1}) as well as its facile conversion into **1** by acid treatment.

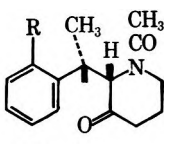
Ketone **1** was readily converted into the pyrrolidine enamine (**5**), which showed only two sharp *singlets* due to the C_2 proton at τ 4.59 and 3.79 with total intensity of one proton in the lower field of the nmr spectrum, confirming the double bond location at C_2 and C_3.[3] Electrophilic substitutions or additions of the enamine were generally carried out by heating with 1 equiv or excess of alkylating reagents in dry dioxane or acetonitrile. The reactions were continued until the starting enamine had disappeared or until the products had started to decompose, and the products after hydrolysis were separated and purified by thin layer (tlc) or column chromatographies. The results are summarized in Table I. The products listed in Table I showed satisfactory elemental analyses as well as uv, ir (ν_{max} *ca.* 1720 and 1636 cm^{-1}), and nmr spectra[7,8] consistent with the assigned structures.[9]



6



7b, R = H
c, R = CH_3



8b, R = H
c, R = CH_3

The alkylated piperidines were produced from enamine **5** in 40–76% yields except in a few cases (runs e and i). These low yields are ascribed to the parallel occurrence of N-alkylations and also of side reactions caused by extremely reactive alkylating reagents. In view of the fact that the starting ketone **1** and resulting piperidines **6** are not very stable, the present yields are regarded as moderate, as compared with those in the corresponding reactions with cyclohexanone.[1c] In summary, the result suggests that the relevant alkylations would be generally available for synthesis.[10]

Experimental Section[9]

Melting points were measured in open capillaries and are uncorrected. Homogeneity of each compound was always checked by tlc on silica gel (Wakogel B-5) and/or alumina (Merck G). The uv and ir spectra were taken in 99% ethanol and in the liquid state, unless otherwise stated. The nmr spectra were determined in deuteriochloroform at 60 and/or 100 MHz, tetramethylsilane being used as an internal reference. The abbreviations "s, d, t, q, m, do, tri, and br" in the nmr spectra denote "singlet, doublet, triplet, quartet, multiplet, double, triple, and broad," respectively.

1-Acetyl-3-oxopiperidine (1).—To a solution of perbenzoic acid (2.85 g, purity 82%) in dry ether (10 ml) was added dropwise 1-acetyl-1,4,5,6-tetrahydropyridine[5] (**2**, 2.00 g) in dry ether (5 ml) under stirring and cooling with a freezing mixture during 2 min, and the mixture was allowed to stand overnight in a refrigerator. The crystalline substance separating out was collected by decantation and washed with cold, dry ether to yield 1-acetyl-2-benzoyloxy-3-hydroxypiperidine (**3**, 2.25 g), mp 101–105°, which was used without further purification, ir (Nujol) ν_{max} 3300, 3025, 1732, 1626, 948, 890, and 715 cm^{-1}.

The hydroxypiperidine **3** (1.00 g) was heated to 140° (oil-bath temperature) under reduced pressure (2 mm) for 1 hr in a sublimation apparatus. The pyrolyzed product adhering to the cold finger was combined with those obtained in another three runs (total 4.0 g), dissolved in ether (100 ml), and mixed with powdered sodium carbonate (10 g) under vigorous stirring, and then filtered to remove the resulting benzoic acid. The filtrate was dried and evaporated to yield oxopiperidine (**1**, 0.71 g) as an oil, which showed the same ir spectrum as the analytical sample. This was distilled to give an analytical sample (550 mg): bp 118–120° (0.21 mm); mass spectrum *m/e* 141 (M^+) and 98; ir 1726 and 1642 cm^{-1}; nmr τ 7.89 and 7.82 (each s, $NCOCH_3$), 7.52 (2 H, m, H at C-), 6.35 and 6.29 (total 2 H, each t, J = 6 and 6 Hz, H at C_6), and 5.97 and 5.83 (each 1 H, s, H at C_2).

(7) H. Paulsen and K. Todt, *Angew. Chem.*, **78**, 943 (1966); *Chem. Ber.*, **100**, 3385, 3396 (1967).

(8) R. A. Johnson, *J. Org. Chem.*, **33**, 3627 (1968).

(9) Representative nmr spectra and interpretation, details of the purification and properties of compounds **6a** to **6k** (Table I) and the preparation of 1-(*o*-tolyl)ethyl bromide will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JOC-72-2343. Remit check or money order for $4.00 for photocopy or $2.00 for microfiche.

(10) For examples of the use of enamines for alkaloid syntheses, see, E. Wenkart, *Accounts Chem. Res.*, **1**, 78 (1968); D. A. Evans, *J. Amer. Chem. Soc.*, **92**, 7593 (1970), and references cited therein.

TABLE II
REACTION CONDITIONS IN ALKYLATIONS OF PYRROLIDINE ENAMINE OF 1-ACETYL-3-OXOPIPERIDINE (1)

Alkylating reagents		Ketone 1		Enamine 5,	Sol-		Temp,	Time,			
Run	mg	equiv[b]	mg	mmol	mg	vent[a]	ml	°C	hr	Products	mg[c]	%[b]
a	758	2.0	423	3.0	586	D	1.5	100	14	6a	301	44
b	532	1.0	424	3.0	584	D	3.0	100	10	7b	235	33
										8b	140	20
c	597	1.0	423	3.0	593	D	3.0	100	10	7c	230	27
										8c	148	17
d	721	2.0	421	3.0	590	A	2.0	70	12	6d	337	62
e	910	1.0	635	4.5	890	D	3.0	100	6	6e	120	13
f	735	1.0	517	3.6	717	D	4.2	100	0.6	6f	692	76
g	480	1.0	494	3.5	678	D	1.5	100	0.25	6g	278	40
h	1001	2.0	425	3.0	588	D	1.5	100	4	6h	280	40
i	445	1.1	710	5.0	960	D	5.0	25	8	6i	59	6
j	896	3.0	426	3.0	558	D	2.0	100	13	6j	334	48
k	1366	4.0	494	3.5	652	D	2.5	100	18	6k	352	52

[a] D, dioxane; A, acetonitrile. [b] Based on ketone 1. [c] Weights of isolated products.

Anal. Calcd for $C_7H_{11}NO_2$: C, 59.55; H, 7.85; N, 9.92. Found: C, 59.43; H, 7.98; N, 9.75.

The pyrolyzed product remaining on the bottom of the apparatus crystallized on trituration with ethanol. This (240 mg) was recrystallized from ethanol to give an analytical sample of dimer **4**: mp 262–264°; mass spectrum *m/e* 282 (M^+) and 141; ir (Nujol) ν_{max} 1650, 1072, and 986 cm^{-1}. This was scarcely soluble in chloroform, dimethyl sulfoxide, and pyridine.

Anal. Calcd for $C_{14}H_{22}N_2O_4$: C, 59.55; H, 7.85; N, 9.92. Found: C, 59.53; H, 7.77; N, 10.27.

Dimer **5** (500 mg) was suspended in chloroform (20 ml) saturated with dry hydrogen chloride and stirred at room temperature for 4 hr. After addition of sodium carbonate followed by filtration, the mixture was evaporated to leave an oily residue (518 mg). This was separated by preparative tlc and then distilled to give **1** (354 mg), which showed the same ir spectrum and retention time (vpc) as the sample obtained by pyrolysis.

General Procedure.—A solution of 1-acetyl-3-oxopiperidine (**1**) (420–710 mg, 3.5–5.0 mmol) and pyrrolidine (1–2 ml) in benzene (20–60 ml) was refluxed for 2–3 hr, water being removed by azeotropization with a Dean–Stark apparatus. The solution was then evaporated to dryness under reduced pressure to leave the enamine **5**, which showed the ir and nmr spectra superimposable over those of the analytical sample and could be used for further reactions. A part of the enamine was distilled for analysis: bp 125–128° (5 mm) (sublimation apparatus); ir ν_{max} 1640 cm^{-1}; nmr τ 8.17 (6 H, m, $CH_2CH_2CH_2CH_2$ and H at C_5), 7.95 and 7.94 (total 3 H, each s, $NCOCH_3$), 7.76 (2 H, t, J = 6 and 6 Hz, H at C_4), 7.07 (4 H, m, CH_2NCH_2), 6.59 and 6.46 (total 2 H, each t, J = 6 and 6 Hz, H at C_6), and 4.59 and 3.79 (0.6 and 0.4 H, each s, H at C_2).

Anal. Calcd for $C_{11}H_{18}N_2O$: C, 68.00; H, 9.34; N, 14.42. Found: C, 67.76; H, 9.25; N, 14.12.

A solution of the enamine **5** and alkylating reagents (1.0–4.0 equiv) in dioxane or acetonitrile was heated (usually steam-bath temperature) in a sealed tube until the starting material had disappeared or until the product had started to decompose. The reaction mixture was then treated with water (1–4 ml) at *ca.* 100° for 0.5–4.0 hr in a sealed tube and evaporated under diminished pressure. The residue was mixed with water (3–6 ml) and extracted with organic solvents (usually chloroform, 4 × 30 ml). The extracts were dried and submitted to further separation. The detailed reaction conditions were tabulated in Table II.

Registry No.—**1**, 34456-78-5; **3**, 34456-79-6; **4**, 34456-80-9; **5**, 34456-81-0; **6a**, 34456-82-1; **6d**, 34456-83-2; **6e**, 34456-84-3; **6f**, 34456-85-4; **6g**, 34456-86-5; **6h**, 34456-87-6; **6i**, 34456-88-7; **6j**, 34456-89-8; **6k**, 34456-90-1; **7b**, 34456-91-2; **7c**, 34456-92-3; **8b**, 34456-93-4; **8c**, 34456-94-5.

Acknowledgments.—The authors are grateful to Mr. S. Shimokawa for the measurement of 60-MHz nmr spectra, to Miss G. Maeda and Mrs. T. Tohma for the microanalysis, and to Miss Y. Imai for the measurement of mass spectra.

Oxidation of Bis(aroylhydrazones) of α-Dicarbonyl Compounds to 1,2,3-Triazolylisoimides. IV. Substituent Effect

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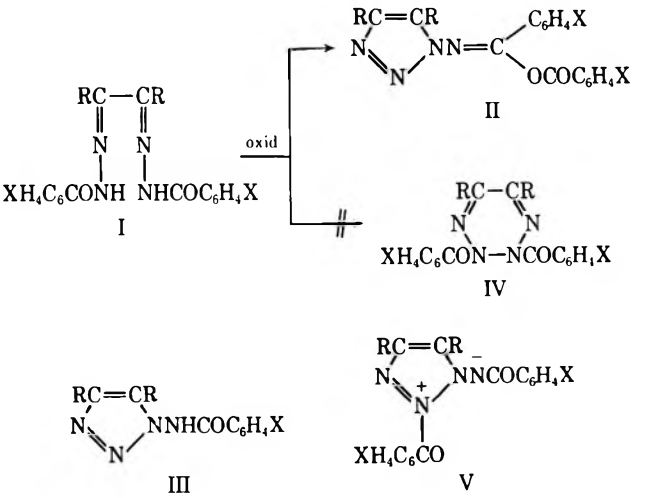
Received December 27, 1971

It is known[2,3] that the oxidation of bis(aroylhydrazones) of α-dicarbonyl compounds I gives, instead of the expected 1,2,3,4-tetrazines IV, 1,2,3-triazolylisoimides II.



The structure of the oxidation products was for a long time in doubt, since the zwitterionic formula V had been also proposed[4,5] as an alternative. However,

(1) Taken in part from the Ph.D. thesis of E. D. M., University of Thessaloniki.

(2) D. Y. Curtin and N. E. Alexandrou, *Tetrahedron.*, **19**, 1967 (1963).

(3) N. E. Alexandrou and E. D. Micromastoras, *Tetrahedron Lett.*, 231 (1968).

(4) Personal communication from Professor A. R. Katritzky (1963).

(5) S. Petersen and H. Heitzer, *Angew. Chem., Int. Ed. Engl.*, **9**, 69 (1970).

TABLE I
OXIDATION PRODUCTS OF BIS(AROYLHYDRAZONES)

Bis(aroylhydrazones) I		Isoimides[a] II		
Compd	Mp, °C	Yield, % (HgO + I_2)	Mp, °C	Ir, cm^{-1}
Ia, R = C_6H_5; X = *p*-Br	265–267	30	178–179	1755, 1635, 1230
Ib, R = C_6H_5; X = *p*-OCH_3	206–208	15	162–163	1745, 1665, 1250
Ic, R = C_6H_5; X = *p*-NO_2	285–287	25	175–176	1765, 1630, 1235
Id, R = CH_3; R′ = *p*-ClC_6H_4; X = *p*-Cl	282–285	60	187–188	1750, 1635, 1240
Ie, R = C_6H_5; R′ = H; X = *p*-Cl	223–226	30	162–163	1750, 1630, 1250
If, R = CH_3; R′ = *p*-$CH_3C_6H_4$; X = H	227–229	35	168–169	1750, 1630, 1230
Ig, R = CH_3; X = *m*-NO_2	>320	15	161–163	1765, 1650, 1230
Ih, R = C_6H_5; X = *m*-NO_2	226–229	20	166–168	1755, 1670, 1240
Ii, R = C_6H_5; X = *m*-CH_3	176–179	50	143–144	1755, 1655, 1260
Ij, R = CH_3; X = *m*-CH_3	277–279	40	120–122	1750, 1650, 1265
Ik, R = C_6H_5; X = *m*-Cl	216–219	40	157–159	1760, 1655, 1235
Il, R = C_6H_5; X = *m*-Br	245–248	50	156–158	1765, 1660, 1235
Im, R = C_6H_5; X = *o*-CH_3	177–179	5	134–135	1750, 1640, 1220
In, R = C_6H_5; X = *o*-Cl	220–222	7	118–119	1752, 1660, 1240
Io, R = C_6H_5; X = *o*-NO_2	286–288			
Ip, R = CH_3; X = *o*-CH_3	284–287	5	76–78	1750, 1640, 1220
Iq, R = CH_3; X = *o*-Cl	306–307	15	108–109	1755, 1660, 1235
Ir, R = C_6H_5; X = *o*-Br	197–199	17	130–131	1753, 1635, 1230

[a] Satisfactory analyses (±0.4% for C, H, N) were reported for all isoimides except IIo and for triazoles IIIm, IIIn, and IIIσ.[b] [b] Other data on triazoles. IIIm: 15% yield; mp 223–224°; ν 3140, 1675 cm^{-1}. IIIn: 5% yield; mp 231–232°; ν 3150, 1685 cm^{-1}. IIIo: <1%; mp 216–218°; ν 3150, 1705 cm^{-1}; mol wt, calcd 385, found *m/e* 385.

recently Katritzky, *et al.*,[6] have shown by an X-ray analysis that the compounds in question are actually isoimides (II).

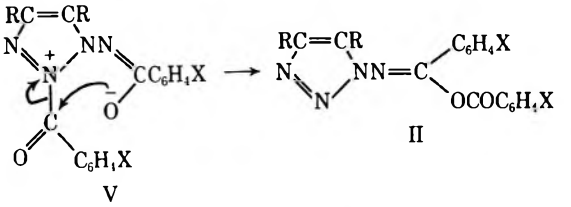
It has been shown[7] previously that the oxidation of bis(aroylhydrazones) to isoimides is sterically influenced and the ortho,ortho′-disubstituted derivatives, especially the bis(mesitoylhydrazones), give instead of II 1-mesitoylamino-1,2,3-triazoles III. In this paper a systematic study of the substituent effect in the oxidation of monosubstituted bis(aroylhydrazones) is made. The aroylhydrazones used as well as their oxidation products are given in Table I.

Oxidation of various meta- or para-monosubstituted bis(aroylhydrazones) Ia–Il with mercuric oxide and iodine[8] gave the expected isoimides II, irrespective of the electronic effect of the substituents X and of the nature of α-diketone used, in yields of 15–60%. In no case were triazole derivatives III formed in isolable amounts.

On the other hand, oxidation of ortho-monosubstituted bis(aroylhydrazones) also gave isoimides, but in yields which, in general, were lower (0–17%) than those from meta or para derivatives, and in some cases 1-aroylaminotriazoles III. The last compounds were obtained from *o*-methyl- and *o*-chlorobis(benzoylhydrazone) of benzil (Im, In), but they were not obtained by oxidation of analogous biacetyl derivatives Ip, Iq, proving thus that the substituents in diketone also influence the oxidation process. The ortho-nitro derivative Io only gave the corresponding benzoylaminotriazole, but in very low yield. Peculiar is the behavior of ortho-bromo derivative Ir, which by oxidation gave isoimide in 17% yield.

In every case of ortho-substituted hydrazones the unoxidized starting material was recovered unchanged.

Although the oxidation of ortho-monosubstituted hydrazones I is actually more complicated than is the oxidation of ortho,ortho′-disubstituted derivatives, it is evident that a steric effect is operating during oxidation, in agreement with the proposed mechanism of isoimide formation (V → II). It is of interest to note that this effect would not be operating if the oxidation products actually had the zwitterionic structure V.



All the isoimides prepared gave in the infrared the characteristic strong ν_{CO} absorption in the region of 1745–1765 cm^{-1}, the absorption position mainly depending[9] on the electronic effect of substituent X. The absorption band is shifted to higher frequencies when the substituent X is an electron-attracting group.

Other characteristic absorptions are found in the regions 1630–1670 ($\nu_{C=N}$, weak) and 1220–1265 cm^{-1} (probably[10] ν_{OC-}, strong). The aroylaminotriazoles showed absorptions at 3140–3150 (ν_{NH}) and 1675–1705 cm^{-1} (ν_{CO}). The nmr spectra of isoimides obtained by oxidation of biacetylbis(aroylhydrazones) always showed two peaks for the C_4 and C_5 methyl protons of the triazole ring at ~τ 7.5 and 7.7.

Although the bis(aroylhydrazones) of unsymmetric α-dicarbonyl compounds (Id, Ie, If) could give by oxidation two isomeric isoimides, in every case only one isomer was isolated and the structure of these products is under further consideration.

The yield of isoimide was increased substantially by using as oxidizing agent, instead of mercuric oxide and iodine, lead tetraacetate in chloroform or in methylene chloride. This oxidizing agent has been

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extensively used for the oxidation of substituted hydrazones and aroylhydrazones.[11-13] The oxidation of bis(aroylhydrazones) Ib, Ie, Ik, Iq, and Ir with lead tetraacetate was carried out by a gentle heating for 2–3 hr. The yields of corresponding isoimides were almost twice those obtained by Stollé's method.[8]

Experimental Section

Melting points are uncorrected and were determined with a Kofler hot-stage apparatus. Ir spectra were measured as Nujol mulls with a Beckman IR-4 or Perkin-Elmer 257 spectrophotometer. Nmr spectra were obtained in $CDCl_3$ with a Varian A-60A spectrometer.

Preparation of Bis(aroylhydrazones) of α Dicarbonyl Compounds.—Those of biacetyl were prepared[14] by heating in ethanol or *n*-propyl alcohol 1 mol of biacetyl with 2.2 mol of the corresponding aroylhydrazines for 6 hr.

The bis(aroylhydrazones) of other α diketones were prepared[15,16] by heating in a sealed tube 1 mol of diketone with 2.2 mol of aroylhydrazines for 12 hr at ~150°. The yields in both methods were 70–90%. The analytical data of the prepared compounds were in agreement with their structure and/or their melting points were in agreement with those of the literature.

Oxidation of Bis(aroylhydrazones) of α-Dicarbonyl Compounds. A. With Mercuric Oxide and Iodine.[8]—A mixture of 0.01 mol of bis(benzoylhydrazone), 0.025 mol of mercuric oxide, 0.025 mol of iodine, and 0.5 g of magnesium oxide in 80 ml of dry ether was heated under stirring for 15 hr. After filtration of the mixture the ethereal solution was washed with potassium iodide solution, then with sodium thiosulfate and water, and finally dried with anhydrous sodium sulfate. The oxidation products were obtained after evaporation and crystallization. The aroylaminotriazoles were separated by fractional crystallization or by chromatographic analysis on aluminum oxide. (For the analytical data of the prepared compound see Table I.) The nonoxidized starting material was recovered by treating the precipitate containing the inorganic material with dilute hydrochloric acid and recrystallization.

B. Oxidation with Lead Tetraacetate.—To a mixture of 0.002 mol of bis(aroylhydrazone) in 20 ml of methylene chloride, a solution of 0.004 mol of lead tetraacetate in 20 ml of methylene chloride was added and the mixture was gently heated for 2–3 hr, or it was left at room temperature for 10 hr. The methylene chloride solution was treated with water, and filtered and the organic layer was washed with sodium bisulfite solution, sodium carbonate solution, and water and then dried. The isoimides were obtained after evaporation and recrystallization. They were identical with those obtained by method A.

Registry No.—Ia, 34502-22-2; Ib, 34502-23-3; Ic, 34502-24-4; Id, 34502-25-5; Ie, 34502-26-6; If, 34502-27-7; Ig, 34502-28-8; Ih, 34502-29-9; Ii, 34502-30-2; Ij, 34502-31-3; Ik, 34502-32-4; Il, 34502-33-5; Im, 34502-34-6; In, 34502-35-7; Io, 34502-36-8; Ip, 34502-37-9; Iq, 34502-38-0; Ir, 34502-39-1; IIa, 34566-67-1; IIb, 19226-34-7; IIc, 34502-40-4; IId, 34502-41-5; IIe, 34502-42-6; IIf, 34502-43-7; IIg, 34502-44-8; IIh, 34502-45-9; IIi, 34502-46-0; IIj, 34519-95-4; IIk, 34502-47-1; IIl, 34519-96-5; IIm, 34502-48-2; IIn, 34502-49-3; IIp, 34599-20-7; IIq, 34502-50-6; IIr, 34519-97-6; IIIm, 34502-51-7; IIIn, 34502-52-8; IIIo, 34502-53-9.

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An Asymmetric Synthesis of Alcohols, Amines, and Amino Acids

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Asymmetric reduction of the ketone moiety has been the subject of much recent investigation.[2] We have reported previously the reduction and reductive amination of aldehydes and ketones using sodium cyanoborohydride ($NaBH_3CN$) as a reducing agent.[3] This new method proved to be especially suitable for the synthesis of isotopically labeled amino acids from the corresponding substituted pyruvic acids. In the hope that we might extend this method to allow preparation of optically active amino acids, we have investigated the use of the structurally similar (*e.g.*, H_3B–X, where X is an electron-withdrawing group) amine–boranes as reducing agents. We were encouraged by a previous report of aldehyde and ketone reduction by the amine–borane system;[4] during the course of our work a detailed study of this reduction appeared.[5] In this report we confirm that both reduction and reductive amination of ketones can be carried out with asymmetric induction to give optically active products, although the optical purities obtained in this synthesis are quite low.

We chose for this study (*R*)(+)- and (*S*)(−)-α-phenethylamine–boranes **2**, which were prepared in 80% yield from the corresponding amine hydrochlorides **1**.[6] The method was initially tested by examining the reduction of acetophenone[7] and 2-heptanone with 1 molar equiv (3 hydride equiv) of amine–borane; the results are summarized in Table I. To ascertain that the rotations were not arising from a trace of α-phenethylamine remaining in the alcohols after work-up, a control experiment was carried out in which alcohol of known optical purity was mixed with (*S*)(−)-α-phenethylamine and subjected to the reaction work-up. The isolated alcohol was free of amine by glpc analysis, and the rotation of the isolated alcohol was identical with that of the starting alcohol. It is apparent that asymmetric reduction did occur, although the optical purities were disappointingly low, presumably owing to the large distance between the asymmetric carbon of the reducing agent and the developing tetrahedral carbon of the product in the transition state. A

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TABLE I

REDUCTION OF 2-HEPTANONE AND ACETOPHENONE WITH (*R*)(+)- OR (*S*)(−)-α-PHENETHYLAMINE–BORANES

Ketone	Confign of 2	Solvent (temp, °C)	Product	Product confign	Product $[\alpha]^{25}D$, degree (*c*, g/100 ml)	Yield, %[a]	Optical purity, %
Acetophenone	*R*(+)	Benzene (reflux)	α-Phenethanol	*R*(+)	+1.80 ± 0.07[b] (6.57)	73	3.3 ± 0.2
Acetophenone	*S*(−)	Benzene (reflux)	α-Phenethanol	*S*(−)	−1.55 ± 0.09[b] (7.23)	66	2.8 ± 0.3
Acetophenone	*R*(+)	CCl_4 (reflux)	α-Phenethanol	*R*(+)	+1.35 ± 0.07[b] (7.49)	76	2.5 ± 0.2
Acetophenone	*R*(+)	Methanol (reflux)	α-Phenethanol	*S*(−)	−0.81 ± 0.07[b] (7.06)	54	1.5 ± 0.1
Acetophenone	*R*(+)	Methanol (25)	α-Phenethanol	*S*(−)	−1.20 ± 0.20[b] (2.74)	58	2.2 ± 0.4
Acetophenone	*S*(−)	Methanol (25)	α-Phenethanol	*R*(+)	+1.04 ± 0.08[b] (7.32)	51	1.8 ± 0.4
2-Heptanone	*R*(+)	Methanol (25)	2-Heptanol	*S*(+)	+0.31 ± 0.04[c] (7.25)	58	2.7 ± 0.4
2-Heptanone	*S*(−)	Methanol (25)	2-Heptanol	*R*(−)	−0.26 ± 0.03[c] (7.05)	51	2.3 ± 0.3
2-Heptanone	*S*(−)[d]	Methanol (25)	2-Heptanol	*R*(−)	−0.23 ± 0.07[c] (2.66)	37	2.2 ± 0.5
2-Heptanone	*S*(−)	Benzene (reflux)	2-Heptanol	*R*(−)	−0.35 ± 0.03[c] (7.36)	76	3.1 ± 0.4
2-Heptanone	*S*(−)	CCl_4 (reflux)	2-Heptanol	*R*(−)	−0.19 ± 0.02[c] (11.40)	91	1.7 ± 0.2

[a] Yields were determined by glpc analysis. [b] Rotations were measured in diethyl ether. [c] Rotations were measured in 95% ethanol. [d] One hydride equivalent of amine–borane **2** was used.

TABLE II

REDUCTION AMINATION OF KETONES WITH (*R*)(+)- AND (*S*)(−)-α-PHENETHYLAMINE–BORANES AND AMMONIA IN METHANOL AT 25°

Ketone	Confign of 2	Product	Product confign	Product $[\alpha]^{25}D$, degree (*c*, g/100 ml)	Yield, %[a]	Optical purity, %
2-Octanone[a]	*R*(+)	2-Octylamine	*S*(+)	+0.45 ± 0.09[b] (2.20)	28	1.6 ± 0.3
2-Octanone[a]	*S*(−)	2-Octylamine	*R*(−)	−0.27 ± 0.09[b] (2.23)	33	1.1 ± 0.3
Pyruvic acid[c]	*S*(−)	Alanine	*S*(+)	+0.32 ± 0.11[d] (3.35)	71	2.2 ± 0.5
2-Ketoglutaric acid[c]	*S*(−)	Glutamic Acid	*R*(−)	−0.97 ± 0.09[d] (3.60)	72	3.1 ± 0.3
Phenylpyruvic acid[c]	*S*(−)	Phenylalanine	*R*(+)	+1.37 ± 0.25[e] (0.81)	66	4.0 ± 0.7
Phenylpyruvic acid[f]	*S*(−)	Phenylalanine-^{15}N[g]	*R*(+)	+1.38 ± 0.35[e] (0.87)	25	4.0 ± 1.0

[a] A 10-fold excess of ammonia was used. [b] The rotation was measured on the benzamide in ethanol. [c] A 5-fold excess of ammonia was used. [d] Rotation was measured in 5 *N* HCl. [e] Rotation was measured in H_2O. [f] 1.2 equiv of $^{15}NH_3$ were used. [g] Isotopic analysis of the product showed >88% ^{15}N.

surprising result was the solvent effect on the product configuration in the case of acetophenone. While the reduction of 2-heptanone afforded a product having an absolute configuration opposite to that of the amine–borane used in all solvents investigated (*i.e.*, *R* amine–borane → *S* alcohol), this observation held only for the reduction of acetophenone in methanol. Reduction of acetophenone in benzene or carbon tetrachloride, however, gave a product with absolute configuration opposite to that obtained in methanol. Unfortunately, the low optical purities (and hence the small transition-state energy differences) observed in these reductions would seem to preclude any meaningful discussion of transition-state complex geometry. It is apparent, however, that these small energy differences are affected by changes in solvation of the complex.

Asymmetric reductive aminations were carried out according to the procedure described earlier,[3] using amine–borane **2** in place of $NaBH_3CN$; the results are summarized in Table II. Yields of amine obtained from 2-octanone are low, owing to the fact that the acid-independent amine–borane reduction[5] of ketone to alcohol is competing effectively with the reductive amination. This was verified by the fact that 2-octanol could be isolated in 30–50% yield from these reductive aminations. Finally, it is interesting to note that the use of amine–boranes in the synthesis of amino acids gives yields appreciably higher than were obtained using sodium cyanoborohydride.[3]

$$\underset{\mathbf{1a,b}}{PhCH(CH_3)NH_2\cdot HCl} \xrightarrow[DME]{NaBH_4} \underset{\mathbf{2a,b}}{PhCH(CH_3)NH_2\text{–}BH_3}$$

a = *R*(+)
b = *S*(−)

$$RCOCH_3 + 2 \longrightarrow \underset{*}{RCH(OH)CH_3}\ (1\text{–}3\%\ \text{optical purity})$$

$$RCOR' + NH_3 + 2 \longrightarrow \underset{*}{RCH(R')NH_2}\ (1\text{–}4\%\ \text{optical purity})$$

Experimental Section[8]

(*R*)(+)- and (*S*)(−)-α-Phenethylamine–boranes (**2a** and **2b**).—To a flame-dried 1-l. flask fitted with a dropping funnel, a nitrogen inlet, and a magnetic stirrer was added 28.3 g (0.18 mol) of (*S*)(−)-α-phenethylamine hydrochloride.[9] The salt was covered with dry dimethoxyethane (distilled from $LiAlH_4$) and cooled in an ice bath, and a solution of sodium borohydride (11.0 g, 0.29 mol) in 500 ml of dimethoxyethane was slowly added over 1.5 hr to the stirred suspension (*CAUTION:* hydrogen evolution occurs throughout the addition). After stirring at 0° for an additional 1.5 hr, the suspension was filtered and the filtrate was evaporated *in vacuo* to give a white semisolid residue. Petroleum ether (100 ml) was added, and the crystalline amine–borane **2b** was collected by filtration (yield 26.8 g). Recrystallization from methylene chloride–petroleum ether afforded

(8) Melting points were obtained in capillary tubes and are uncorrected. Analytical and preparative gas chromatograms were obtained on a Varian Aerograph 90-P3 instrument using 0.25 in. × 10 ft columns. All identifications by glpc analysis were made by peak enhancement with authentic samples. Optical rotations were obtained on a Perkin-Elmer Model 141 polarimeter in a 1-dm cell; concentrations *c* are expressed in g/100 ml. Elemental analyses were performed by the Microanalytical Laboratory, University of Minnesota. Anhydrous magnesium sulfate was used as drying agent throughout.

(9) Available in 97.5% optical purity from Aldrich Chemical Co.

(bp 30–60°) 19.8 g (82%) of **2b**: mp 119–120°; $[\alpha]^{25}D$ −77.2° (c 1.84, benzene); 97.5% optically pure.

Anal. Calcd for $C_8H_{14}BN$: C, 71.13; H, 10.47; N, 10.39. Found: C, 71.09; H, 10.29; N, 10.35.

(*R*)(+)-α-Phenethylamine–borane (**2a**) was prepared in 78% yield as described above: mp 119–120°; $[\alpha]^{25}D$ +77.3° (*c* 2.12, benzene).

Reduction of Ketones with 2a and 2b. General Procedure.—To a solution of the ketone (4 mmol) in 20–25 ml of the appropriate solvent was added 4 mmol of **2a** or **2b** (97.5% optically pure), and the resulting solution was stirred for 4 hr at the specified temperature. The solvent was removed *in vacuo*, and the residue was stirred with excess 6 *N* HCl until no further hydrogen evolution (from hydrolysis of unreacted amine–borane) was observed. The aqueous solution was saturated with sodium chloride and extracted with 3 20-ml portions of ether. The combined extracts were washed with 10-ml portions of 3 *N* HCl, 6 *N* NaOH, and brine, and the ether solution was then dried and evaporated *in vacuo*. The colorless residual oil was analyzed by glpc (15% FFAP on Chromosorb W and 15% Carbowax 20M on Chromosorb W). A sample was purified by preparative glpc, and the optical rotation was measured on this purified sample as a solution in ether (α-phenethanol) or 95% ethanol (2-heptanol). Absolute configuration and optical purity were determined from the known values of $[\alpha]^{25}D$ +54.86° (ether) for (*R*)(+)-α-phenethanol[10] and $[\alpha]^{25}D$ −11.4° (EtOH) for 2-heptanol.[11]

Reductive Amination of 2-Octanone with 2a or 2b and Ammonia.—A solution of 2-octanone (2.24 g, 17.5 mmol) was dissolved in 50 ml of methanol containing ammonia (3.2 ml of liquid NH_3, 140 mmol) and ammonium bromide (3.43 g, 35 mmol), and either **2a** or **2b** (2.36 g, 17.5 mmol) was added. The resulting solution was stirred at 25° for 48 hr. The methanol was removed *in vacuo*, and the residue was stirred for 10 min with excess 6 *N* HCl. The aqueous solution was washed with two 10-ml portions of ether (2-octanol could be isolated from this ether extract if desired). Solid potassium hydroxide was added to the aqueous layer until the pH of the solution was >12, and the amines were extracted with three 25-ml portions of ether. The combined extracts were dried and evaporated *in vacuo* to give a mixture of α-phenethylamine and 2-octylamine. A sample of 2-octylamine was isolated by preparative glpc (15% FFAP on Chromosorb W) and was converted to its benzamide, mp 78–79.5° (86% yield). Absolute configuration and optical purity were determined by comparison of the rotation of the benzamide with the literature value[12] for (*R*)(−)-2-octylamine benzamide of $[\alpha]^{25}D$ −28.5° (EtOH).

Reduction Amination of α-Keto Acids with 2a or 2b and Ammonia. General Procedure.—To a solution of 0.9 ml (40 mmol) of liquid ammonia and 0.98 g (10 mmol) of ammonium bromide in 30 ml of methanol was added 5 mmol of α-keto acid or α-keto acid sodium salt. The resulting solution was stirred for 1 hr at 25°. (*S*)(−)-α-Phenethylamine–borane (0.68 g, 5 mmol) was added, and the solution was stirred at 25° for 36–72 hr. Methanol and excess ammonia were removed *in vacuo*, and the residue was brought to pH 1 with 12 *N* HCl. After stirring for 15 min, the acidic solution was made basic with excess ammonium hydroxide and washed with two 15-ml portions of ether (ether wash discarded). The aqueous solution was evaporated *in vacuo*. The residue was dissolved in a minimum volume of distilled water and added to the top of a Dowex 50 column (acid form, 250-mequiv capacity). The column was washed with 1 l. of distilled water, and the amino acid was then eluted with 250 ml of 2 *N* ammonium hydroxide. The ammonium hydroxide solution was evaporated *in vacuo* to give the amino acid as a colorless solid. Tlc analysis on cellulose and silica gel plates (butanol–acetic acid–water, 4:1:1) showed one spot identical with that of an authentic sample (detected by ninhydrin staining). Absolute configuration and optical purity were determined by comparison of the rotation of the amino acids with the published values: (*S*)(+)-alanine, observed $[\alpha]^{25}D$ +0.32 ± 0.11° (*c* 1.85, 5 *N* HCl), lit.[13] $[\alpha]^{25}D$ +14.6° (5 *N* HCl); (*R*)(−)-glutamic acid, observed $[\alpha]^{52}D$ −0.97 ± 0.09° (*c* 3.60, 5 *N* HCl), lit.[14] $[\alpha]^{25}D$ −31.8° (5 *N* HCl); (*R*)(+)-phenylalanine, observed $[\alpha]^{25}D$ +1.37 ± 0.25° (*c* 0.81, H_2O), lit.[15] $[\alpha]^{25}D$ +34.5° (H_2O).

Phenylalanine-^{15}N.—Sodium phenylpyruvate (0.47 g, 2.5 mmol), ammonium nitrate-^{15}N (0.40 g, 5.0 mmol, 95% $^{15}NH_4NO_3$), and **2b** (0.68 g, 5 mmol) were allowed to react for 36 hr and worked up as described above to give 105 mg (25%) of phenylalanine, $[\alpha]^{25}D$ +1.38 ± 0.35° (*c* 0.87, H_2O). A sample was purified by preparative tlc (silica gel G, 4:1:1 butanol–acetic acid–water) for nitrogen isotope mass spectral analysis, minimum ^{15}N composition 88%.[16]

Registry No.—**2a**, 34566-00-2; **2b**, 34566-01-3; 2-heptanone, 110-43-0; acetophenone, 98-86-2; (*R*)-(+)-α-phenethanol, 1517-69-7; (*S*)(−)-α-phenethanol, 1445-91-6; (*S*)(+)-2-heptanol, 6033-23-4; (*R*)(−)-2-heptanol, 6033-24-5; (*S*)(+)-2-octylamine, 34566-04-6; (*R*)(−)-2-octylamine, 34566-05-7; (*S*)(+)-alanine, 3081-24-1; (*R*)(−)-glutamic acid, 6893-26-1; (*R*)(+)-phenylalanine, 673-06-3; (*R*)(+)-phenylalanine-^{15}N, 673-06-3.

(10) B. Angelo and G. Vavon, *C. R. Acad. Sci.*, **224**, 1435 (1947).
(11) "Handbook of Chemistry and Physics," 50th ed, 1969, p C-323.
(12) P. A. Levene, A. Ruthen, and M. Kuna, *J. Biol. Chem.*, **120**, 759 (1937).
(13) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 3, Wiley, New York, N. Y., 1961, p 1819.
(14) Reference 13, p 1929.
(15) Reference 13, p 2156.
(16) We thank Adrian Swanson, University of Minnesota Mass Spectrometer Laboratory, for this determination.

Pyrolysis of 2-Acetoxy-2-methylcyclopentane-1,3-dione and 3-Acetoxy-3-methylpentane-2,4-dione

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Pyrolysis of 2-acetoxy-2-alkylcyclohexane-1,3-diones (**1–3**) at ~220° for 3–4 hr affords 60–80% of the related 2-alkylcyclopenten-2-ones (**4–6**), plus acetic acid and carbon monoxide.[1,2] It was of interest to see if this remarkably efficient thermal ring contraction reaction could be extended to other types of 2-acetoxy-2-alkyl-1,3-diones. This paper describes the synthesis and pyrolysis of 2-acetoxy-2-methylcyclopentane-1,3-dione (**7**) and 3-acetoxy-3-methylpentane-2,4-dione (**8**). If an analogous ring contraction were to occur, **7** would yield the as yet unreported 2-methylcyclobutenone (**9**) and provide the prototype of a new synthesis of cyclobutenones. The analogous reaction of **8** would yield methyl isopropenyl ketone (**10**) and perhaps provide a useful method for the synthesis of alkyl vinyl ketones.

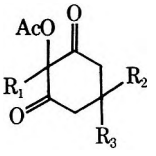
The preparation of **7** was accomplished by the reaction of 2-methylcyclopentane-1,3-dione (**11**)[3] with lead tetraacetate, in the same manner as the preparations of **2** and **3**,[2] but the maximum yield of pure **7** was only 3%. Exploration of alternate routes, such as thallium triacetate oxidation[4] of enamines **12** and **13**,[5] or epoxidation of enol acetate **14**,[6] in the hope of ther-

(1) T. A. Spencer, S. W. Baldwin, and K. K. Schmiegel, *J. Org. Chem.*, **30**, 1294 (1965).
(2) T. A. Spencer, A. L. Hall, and C. F. von Reyn, *ibid.*, **33**, 3369 (1968).
(3) V. J. Grenda, G. W. Lindberg, N. L. Wendler, and S. H. Pines, *ibid.*, **32**, 1236 (1967).
(4) M. E. Kuehne and T. J. Giacobbe, *ibid.*, **33**, 3359 (1968).
(5) J. J. Panouse and C. Sannié, *Bull. Soc. Chim. Fr.*, 1374 (1956).
(6) B. D. Challand, H. Hikino, G. Kornis, G. Lange, and P. de Mayo, *J. Org. Chem.*, **34**, 794 (1969); D. J. Crispin, A. E. Vanstone, and J. S. Whitehurst, *J. Chem. Soc. C*, **10**, (1970).

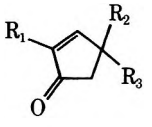
mally rearranging the product to **7**,[7] was unpromising; so sufficient **7** for pyrolysis studies was accumulated by the inefficient direct acetoxylation of **11**.

Compound **7**, mp 62–63°, underwent no change upon being heated at 220° for 1 hr. At 350–400° it reacted to form a distillate of acetic acid (no evidence of **9**) and a pot residue of solid black tar. Effluent gases were trapped and shown by vpc analysis to contain less than 7.5% of the carbon monoxide which would be produced by **7** → **9**, plus an almost equal amount of methane, which had never been detected in earlier pyrolyses.[1,2]

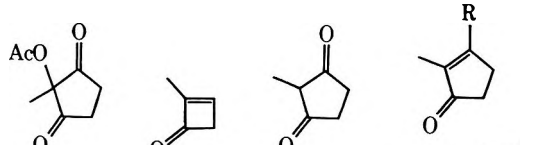
Compound **8**, mp 26–27°, was also prepared by lead tetraacetate acetoxylation of the appropriate dione **15**



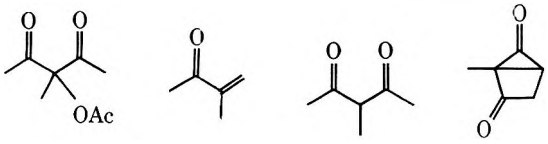
1, $R_1 = CH_2CH_2COCH_3$; $R_2 = R_3 = H$
2, $R_1 = CH_3$; $R_2 = R_3 = H$
3, $R_1 = R_2 = R_3 = CH_3$



4, $R_1 = CH_2CH_2COCH_3$; $R_2 = R_3 = H$
5, $R_1 = CH_3$; $R_2 = R_3 = H$
6, $R_1 = R_2 = R_3 = CH_3$



7 **9** **11** **12**, R = N **13**, R = N O **14**, R = OAc



8 **10** **15** **16**

in *ca.* 30% yield. Far from reacting at its boiling point (222°), **8** was essentially completely stable at 320° for 4.5 hr. At 380–400° it reacted to form acetic acid (*ca.* 95%) and a dark residue. No evidence of **10** was obtained, and, again, only a small fraction of the amount of carbon monoxide which would have been produced by the formation of **10** was detected.

The failure of **7** to undergo conversion to **9** is of course explicable on the basis of the ring strain inherent in the product, particularly if the ring contraction proceeds, as is suspected,[2,8] *via* initial 1,3 elimination of acetic acid to form a cyclopropanone, which in the present case would be the very strained bicyclo[2.1.0]dione **16**. It is less obvious why the reaction of **8** to form **10** does not occur. 2-Acetoxy-2-alkylcyclohexane-1,3-diones are clearly, perhaps uniquely, predisposed toward such extrusion of carbon monoxide and acetic acid. Even with this class of compounds, the reaction is severely limited as a method of preparing cyclopentenones by the low yields in the acetoxylation step.[9]

(7) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, pp 120–121.

(8) R. G. Carlson and J. E. Bateman, *J. Org. Chem.*, **32**, 1608 (1967).

Experimental Section[10]

2-Acetoxy-2-methylcyclopentane-1,3-dione (7).—The 2-methylcyclopentane-1,3-dione (**11**) used in the acetoxylation was prepared by the method of Grenda, Lindberg, Wendler, and Pines,[3] and the lead tetraacetate was prepared, purified, and stored according to the procedure of Fieser.[11] A wide variety of solvents and experimental conditions for the reaction of **9** with lead tetraacetate were tried. Based on previous experience with this type of reaction,[2] we favored conditions, such as those described below, in which only a small amount of the **9** was dissolved, in an attempt to minimize formation of dehydrodimeric products. To a mixture of 30.0 g (0.268 mol) of **9**, mp 211–214°, 20 ml of acetic acid, 20 ml of acetic anhydride, and 1000 ml of benzene in a 2-l. flask was added 120 g (0.27 mol) of lead tetraacetate. The flask was covered to keep light out and was stirred overnight. The reaction mixture was filtered to remove 73 g (0.22 mol, 83%) of precipitated lead diacetate. The filtrate was evaporated to a yellow oil to which was added 500 ml of anhydrous ether, producing a yellow, ethereal solution and a yellow, solid residue. The ethereal solution was evaporated and its residue was chromatographed on 700 g of Florisil. Careful elution with 3:7 ether–hexane gave 1.86 g (4%) of crude **7**, which was purified by vacuum sublimation to afford 1.30 g (3%) of **7**, mp 59–60°. An analytical sample of **7** prepared by recrystallization from ether had mp 62–63°; ir (KBr) 5.75 μ; nmr ($CDCl_3$) δ 1.37 (s, 3, $H_3CC<$), 2.10 (s, 3, H_3CCOO-), and 2.86 ppm (s, 4, $-CH_2CH_2-$).

Anal. Calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92. Found: C, 56.40; H, 5.89.

No attempt was made to purify or characterize other products from this reaction, although spectra of crude fractions suggested the presence of dehydrodimeric compounds analogous to those found previously.[2]

Pyrolysis of 7.—Using an apparatus of the type previously described,[1] 4.023 g (0.0236 mol) of **7** in a 10-ml flask was heated at a pot temperature of 220–250° at atmospheric pressure, and with a stream of nitrogen bubbling through it was refluxed through a heating column at *ca.* 370°. A liquid condensed in the apparatus above the heating column which was identified as acetic acid by its ir spectrum. After 35 min, during which time the material in the flask turned black, boiling had essentially ceased. The cooled residue in the flask was 2.027 g of black solid, ir (KBr) 5.90 and 6.2–6.4 μ. Effluent gas, including the nitrogen run through the system, had been collected throughout the pyrolysis. Vpc analysis of this 800 ml of gas on a 5A molecular sieve column[1] showed that it contained less than 5% carbon monoxide (identified by comparison of its retention time with known carbon monoxide prepared by reaction of formic and sulfuric acids), which corresponded to formation of less than a 7.5% yield from **7**. The trapped gas also contained a somewhat lesser amount of methane (identified by comparison of its retention time with that of known methane prepared by reaction of methyllithium with water), nitrogen, and oxygen.

3-Acetoxy-3-methylpentane-2,4-dione (8).—3-Methylpentane-2,4-dione (**15**) was prepared by the methylation of pentane-2,4-dione by the procedure of Johnson, Markham, and Price.[12] Vpc analysis of the product, bp 168–169°, showed that it was a 4:1 mixture of **15** and 3,3-dimethylpentane-2,4-dione, which was used without purification in the acetoxylation. A solution of

(9) *Cf.* G. Büchi and B. Egger, *J. Org. Chem.*, **36**, 2021 (1971), for a closely related, more effective synthesis of cyclopentenones.

(10) The analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Melting points were taken in an open capillary and are uncorrected. Ir spectra were taken on a Perkin-Elmer Model 137 spectrometer. Nmr spectra were obtained on a Varian Model DA-60-IL instrument. Uv spectra were obtained on a Unicam Model SB 800 spectrometer. Vpc was done on a Wilkens Model A 700 chromatograph.

(11) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath, Boston, Mass., 1955, pp 325–326.

(12) A. W. Johnson, E. Markham, and R. Price, *Org. Syn.*, **42**, 75 (1962); *cf.* **45**, 68 (1965).

80.3 g of this product, containing *ca.* 62.7 g (0.55 mol) of **15**, in 350 ml of dry benzene was added dropwise over 4 hr to 1 l. of dry benzene, to which was added at the beginning of the reaction and at hourly intervals *ca.* one-fourth of a total of 250 g (0.569 mol) of lead tetraacetate.[11] The reaction was exothermic and maintained itself at *ca.* 35–40°. The yellow reaction mixture was filtered to remove lead diacetate, which was washed with 4 × 100 ml of benzene. The combined benzene layers were washed with 4 × 1 l. of water, dried over sodium sulfate, filtered, and evaporated. The 153.2 g of residue was distilled under reduced pressure to afford benzene (78 g), starting material (4 g), and 58 g, bp 70–165° (3.5–5.5 mm), which was redistilled to afford 17.1 g of starting material, bp 32–45° (1–2 mm), and 29.1 g (31%) of crude **8**, bp 85–145° (1.5–2.5 mm). When placed in the freezer with a small amount of ether, this product solidified to afford, after recrystallization from ether in the cold, 13.4 g (14%) of pure **8**: mp 26–27°; bp 222°; uv max (cyclohexane) 299 mμ (ε 84); ir (film) 5.70 and 5.80 μ; nmr ($CDCl_3$) δ 1.67 (s, 3, H_3C–C<), 2.12 (s, 3, H_3CCOO–), and 2.18 ppm (s, 6, 2 H_3CCO–).

Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.69; H, 6.90.

Pyrolysis of **8**.—Using an apparatus of the type previously described,[1] 9.74 g (0.056 mol) of **8** in a 25-ml flask was refluxed at a pot temperature of 240° through a heating column at 380–400° for 7 hr. There was obtained 3.94 g of yellow distillate and a dark, solid pot residue. The distillate was found by vpc analysis to be *ca.* 75% acetic acid (*ca.* 95% yield), *ca.* 10% **8**, and *ca.* 15% of an unidentified substance which was not **10**. Ultraviolet spectra of all product fractions indicated that **10** was not present in significant amounts. Effluent gas, including the nitrogen run through the system, was collected during much of the pyrolysis. Vpc analysis of this gas indicated that a maximum of 25% of the theoretical amount of carbon monoxide required for formation of **10** could have been produced.

Registry No.—**7**, 34564-51-7; **8**, 34564-52-8; **9**, 34564-53-9; **15**, 815-57-6.

Acknowledgment.—R. A. A. was a recipient of financial support under the terms of an institutional research training grant from the U. S. Public Health Service, summer, 1971.

A Rational Synthesis of 2-Aminoindazole

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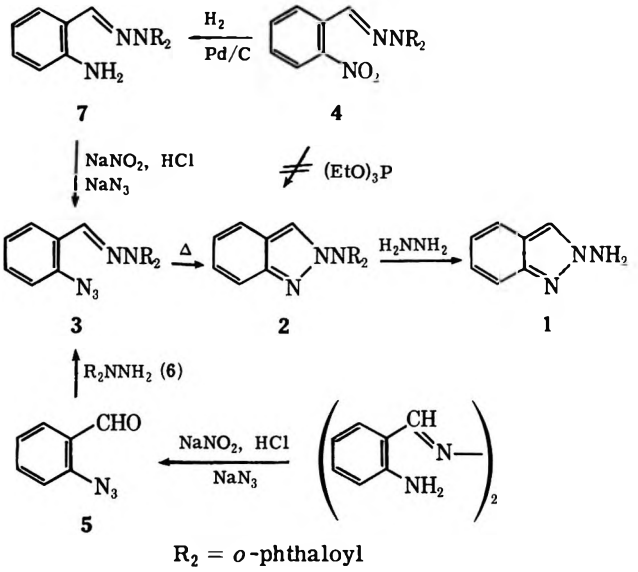
Received December 29, 1971

As a part of our investigation of the chemistry of *N*-nitrenes,[2] it was of interest to study the oxidation of 2-aminoindazole (**1**). This report of the rational synthesis of **1** and of its oxidation is prompted by the recent disclosure of the preparation of both 1- and 2-aminoindazole by the amination of indazole with hydroxylamine-*O*-sulfonic acid.[3]

The scheme used for the preparation of **1** is based on the cyclization of an *o*-nitreno benzaldimine derivative.[4a,b] The failure of our initial attempts to deoxygenate *N*-(*o*-nitrobenzal)aminophthalimide (**4**) to **2**[4] led us to generate the nitrene from the corresponding azide. In this fashion, **1** was obtained in 94% yield from **3** as yellow crystals, mp 96–97°, as illustrated in Scheme I.

SCHEME I



R_2 = *o*-phthaloyl

Although **3** was also prepared by the diazotization and azidation of **7**, it was best obtained by the condensation of *o*-azidobenzaldehyde (**5**) with *N*-aminophthalimide (**6**). *o*-Azidobenzaldehyde was synthesized in one step by the diazotization and azidation of *o*-aminobenzaldazine.

Since Rees and his group[3,5] have extensively investigated the oxidation of **1**, we will only briefly describe our results carried out under different experimental conditions. Besides trace amounts of indazole (**12**), 2,2′-biindazole (**13**) was the main product obtained from the oxidation of **1** with mercuric oxide in refluxing *n*-butyl alcohol for 96 hr; in addition, an unstable crude compound exhibiting absorption in the triple bond region was also isolated as a very minor component which may perhaps be the product of the fragmentation of the *N*-nitrene. Addition of a catalytic amount of sodium methoxide gave essentially the same results, although only 2 hr were required in this case. In benzene at room temperature, oxidation with lead tetraacetate gave **12**.

Our results, in conjunction with those of Rees and his students,[3,5] indicate that, under those conditions, fragmentation of 2-indazolyl nitrene (**8**) is not favored, occurring at best only to a minor extent. In view of the difference between Rees' results[2] and ours, it seems likely that the formation of the tetrazane **10**[6] and of the tetrazene **11** does not proceed *via* the *N*-nitrene **8**. Scheme II cutlines possible routes which may help explain the products obtained by us. Evidently, the conditions of our oxidations would preclude any possibility of isolation of the 1,2,3-benzotriazine isolated by Rees only in the strict absence of nucleophiles.[3]

(1) Fellow of the A. P. Sloan Foundation.

(2) K. Sakai and J.-P. Anselme, *Tetrahedron Lett.*, 3851 (1970); K. Sakai, A. Tanaka, G. Koga, and J.-P. Anselme, *J. Chem. Soc. Jap., Pure Chem. Sect.*, **92**, 1065 (1971).

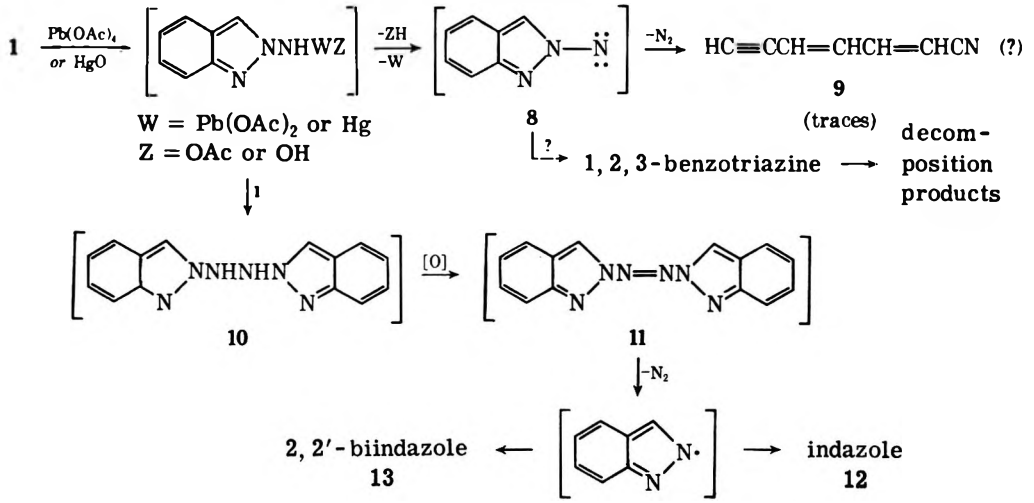
(3) D. J. C. James, S. Bradbury, D. C. Horwell, M. Keating, C. W. Rees, and R. C. Storr, *Chem. Commun.*, 828 (1971).

(4) (a) L. Krbechek and H. Takimoto, *J. Org. Chem.*, **29**, 1150 (1964); (b) P. A. S. Smith in "Nitrenes," W. Lwowski, Ed., Wiley, New York, N. Y., 1970, p 139; (c) J. I. G. Cadogan and R. J. G. Searle, *Chem. Ind. (London)*, 1282 (1963).

(5) Private communication from C. W. Rees.

(6) D. J. Anderson, T. L. Gilchrist, and C. W. Rees, *Chem. Commun.*, 800 (1971).

SCHEME II



Experimental Section[7]

N-(*o*-Nitrobenzal)aminophthalimide (4) was prepared in 90% yield by overnight reflux of equimolar amounts (0.1 mol) of *N*-aminophthalimide and *o*-nitrobenzaldehyde in 250 ml of ethanol containing a catalytic amount of acetic acid. The pale yellow analytical sample, mp 227–229°, was obtained by crystallization from benzene–ethanol.

Anal. Calcd for $C_{15}H_9N_3O_4$: C, 61.02; H, 3.07; N, 14.23. Found: C, 60.99; H, 3.22; N, 14.12.

N-(*o*-Aminobenzal)aminophthalimide (7), mp 189–191°, was obtained in 90% yield by hydrogenation of 4 over Pd/C in ethanol until the theoretical amount of hydrogen was absorbed. The analytical sample was obtained as pale yellow crystals after crystallization from benzene–ethanol.

Anal. Calcd for $C_{15}H_{11}N_3O_2$: C, 67.91; H, 4.18; N, 15.84. Found: C, 68.04; H, 4.30; N, 15.53.

N-(*o*-Azidobenzal)aminophthalimide (3) was synthesized by diazotization of 7 with sodium nitrite in a mixture of acetic acid and hydrochloric acid, followed by the addition of sodium azide. The yield of product, identical with material prepared by the alternate route described below, was 34%.

Compound 3 was also obtained in 67% yield by the condensation of *o*-azidobenzaldehyde with *N*-aminophthalimide in the presence of catalytic amounts of acetic acid in ethanol. Recrystallization from ethanol–benzene gave the analytically pure pale yellow sample, mp 170–171°.

Anal. Calcd for $C_{15}H_9N_5O_2$: C, 61.85; H, 3.12; N, 24.05. Found: C, 61.77; H, 3.32; N, 24.10.

o-Azidobenzaldehyde (5).—*o*-Aminobenzaldazine (31 mmol) was diazotized at 0° in a mixture of 150 ml of acetic acid and 50 ml of concentrated hydrochloric acid by the addition of an aqueous solution of 87 mmol of sodium nitrite in 30 ml of water. The mixture was stirred for 0.5 hr at 0°, then an aqueous solution of 130 mmol of sodium azide in 40 ml of water was slowly added while the temperature was kept at 0°. Stirring was continued for an additional 0.5 hr at that temperature, then for 15 min at room temperature. After addition of 200 ml of water and extraction with ether, the ethereal extract was washed successively with water, 5% sodium hydroxide solution, and water. The organic phase was dried and evaporated to give 4.3 g (48%) of *o*-azidobenzaldehyde, mp 34–36° (lit.[8] mp 35–36.5°).

2-(*N*-Phthalimido)indazole (2).—Cyclization of 1 g of 3 was achieved by heating in 60 ml of *o*-dichlorobenzene at 140–145° for 1.5 hr. After the evolution of nitrogen had subsided, the solvent was removed at ~100° under reduced pressure. Recrystallizaof the residue from benzene–ethanol gave 0.81 g (97%) of white product, mp 262–263°.

Anal. Calcd for $C_{15}H_9N_3O_2$: C, 68.43; H, 3.44. Found: C, 68.13; H, 3.65.

2-Aminoindazole (1).—A solution of 4.5 g (0.017 mol) of 2 in 150 ml of ethanol containing an excess (2.1 g) of hydrazine was warmed for ~0.5 hr; a white precipitate was formed very rapidly. Then an excess of concentrated hydrochloric acid was added and the mixture was again warmed for ~15 min. The insoluble phthalhydrazide (1.89 g) was filtered and the filtrate was concentrated to remove the alcohol. The residue was then made alkaline with concentrated ammonium hydroxide and extracted with several portions of ether. The ethereal extract was dried and evaporated to give 2.19 g (97%) of essentially pure 2-aminoindazole as very pale yellow crystals, mp 95–96°. Recrystallization from benzene–ethanol (9:1) gave the analytically pure sample, mp 96–97°.

Anal. Calcd for $C_7H_7N_3$: C, 63.14; H, 5.29; N, 31.56. Found: C, 63.38; H, 5.22; N, 31.59.

Oxidation of 2-Aminoindazole. A. Yellow Mercuric Oxide.—A mixture of 0.25 g (1.9 mmol) of 1 and 0.50 g (2.3 mmol) of yellow mercuric oxide in 30 ml of *n*-butyl alcohol was heated to reflux for 4 days; during this time, a total of 43 ml of gas was collected. Evaporation of the solvent gave a solid–liquid mixture whose infrared spectrum exhibited absorption in the triple-bond region (–CN?). Crystallization of this mixture from benzene gave 0.15 g of yellow crystals, mp 254–256°, which upon several recrystallizations from benzene–ethanol gave a pure sample of 2,2'-biindazole, mp 267–268° dec (lit.[3] mp 268°). Work-up of the filtrate gave trace amounts of recovered 1 and of indazole, which was isolated by sublimation and identified as its picrate, mp 134–136° (lit.[9] mp 136°).

When a catalytic amount of sodium methoxide was added, essentially the same results were obtained in 2 hr instead of 4 days.

B. Lead Tetraacetate.—A mixture of 0.65 g (4.9 mmol) of 1 and 2.2 g of lead tetraacetate in 25 ml of benzene was stirred at 0° until the initial reaction had subsided, then at room temperature for 40 min, and finally heated at reflux for an additional 20 min. The precipitated lead diacetate was removed and washed with ether. The combined filtrate was washed successively with water, 10% sodium bicarbonate solution, and water. Evaporation of dried solution *in vacuo* left 0.45 g of a reddish mass. Sublimation of part of this material showed it to consist essentially of indazole, identified as its picrate.

Registry No.—1, 33334-11-1; 2, 34638-59-0; 3, 34638-60-3; 4, 32387-06-7; 5, 16714-25-3; 7, 34608-92-9.

Acknowledgment.—The generous support of this work by the National Institutes of Health under Grant GM 13689-05 is hereby acknowledged with deep appreciation.

(7) All melting points are uncorrected. Analyses were performed by the Microchemical Laboratory of Belmont, Mass.

(8) E. Bamberger and E. Demerth, *Ber.*, **34**, 1334 (1901).

(9) E. Fischer and O. Seuffert, *Ber.*, **34**, 797 (1901).

The Sulfuric Acid Catalyzed Cyclization of *N*-(*trans*-Cinnamyl)-*p*-nitrobenzamide[1]

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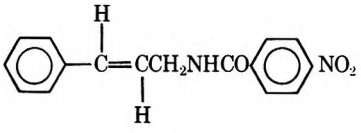
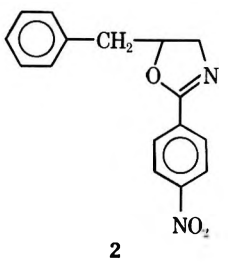
Kashelikar and Fanta[2] reported that treatment of *N*-(*trans*-cinnamyl)-*p*-nitrobenzamide (**1**) with 95% sulfuric acid gave a new compound which was assigned the oxazoline structure **2** solely on the basis of an elemental analysis and the lack of a NH band in the infrared absorption spectrum.

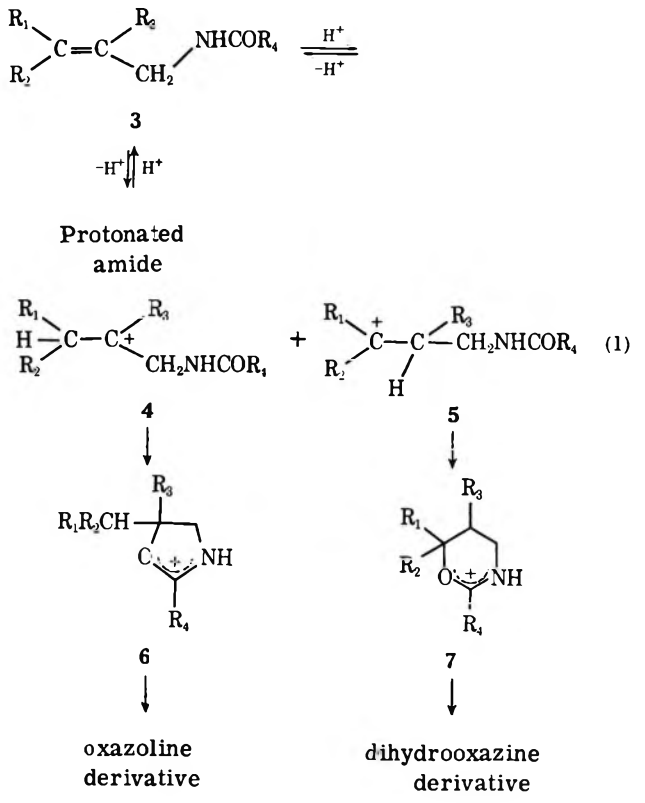


1



2

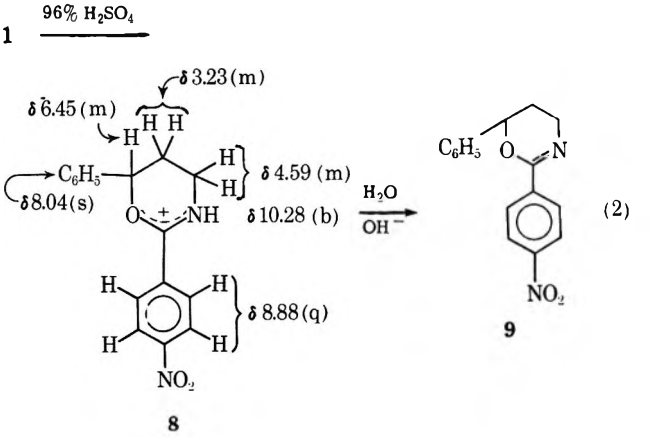
Our recent results[3] suggest that cyclizations of allylic amides in strongly acidic media occur through open carbonium ions (eq 1) instead of proceeding with amide neighboring group participation. Our mechanism would also predict that the major product from such cyclizations would form through the more stable carbonium ion. For example, **3** ($R_1 = R_2 = H$; $R_3 = CH_3$) leads exclusively to **6**, presumably through cation **4**. One would expect that proper substitution for R_1, R_2, and R_3 in **3** could shift the product toward **7** through cation **5**. With R_1 = phenyl and $R_2 = R_3 = H$ in **3**, the expectation of getting **7** (R_1 = phenyl; $R_2 = R_3 = H$) should be realized.



3 **Protonated amide** **4** **5** **6** **7** **oxazoline derivative** **dihydrooxazine derivative**

(1)

In accordance with this prediction, we found that the nmr spectrum[4] measured after dissolving **1** in 96% sulfuric acid consists of broad multiplets at δ 3.23 (2 protons), 4.59 (2 protons), and 6.45 (1 proton), a sharp singlet at δ 8.04 (5 protons), an A_2B_2 quartet centered at δ 8.88, and a broad peak at δ 10.28 (1 proton). Irradiation of the two-proton multiplet at δ 3.23 caused the spectrum of the proton at δ 6.45 to collapse to a singlet. No other changes in the spectrum occurred. Other than those peaks mentioned, the spectrum was clean. These nmr data fully support the sole formation of the 2-*p*-nitrophenyl-6-phenyl-5,6-dihydro-1,3-oxazinium ion (**8**) in this cyclization reaction (eq 2).



8 **9**

(2)

Since rearrangement upon isolation is highly unlikely,[3a] our findings suggest that **1** cyclizes to the oxazine **9** and not to **2** as proposed by Kashelikar and Fanta.[2]

On the basis of these findings, the material prepared more than 12 years ago by Kashelikar,[2] and previously assigned structure **2**, was reexamined. In a capillary melting point tube, it sintered at 112° and melted to a slightly turbid liquid at 113–115°, indicating that only slight decomposition or polymerization had occurred on prolonged standing. A solution of the compound in $CDCl_3$ was filtered to remove a trace of suspended

(1) (a) Acid-catalyzed Cyclization Reactions. X. For previous papers in the series, see S. P. McManus, J. T. Carroll, and C. U. Pittman, Jr., *J. Org. Chem.*, **35**, 3768 (1970). (b) S. P. M. thanks the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

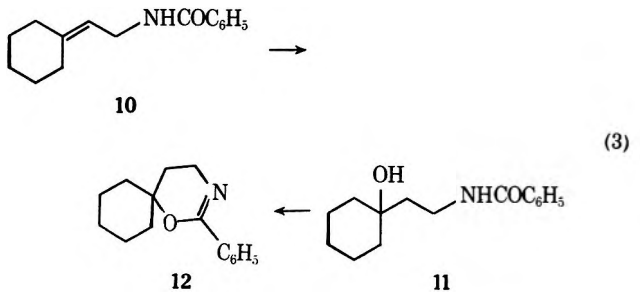
(2) D. V. Kashelikar and P. E. Fanta, *J. Amer. Chem. Soc.*, **82**, 4930 (1960).

(3) (a) See ref 1a; (b) S. P. McManus, B. P. Allen, J. F. Sisson, C. R. Taddei, and C. U. Pittman, Jr., unpublished results.

(4) Nmr spectra were measured in $CDCl_3$ with an internal TMS standard or in sulfuric acid with an external TMS standard (capillary). Either a Varian A-60, HA-100, or Bruker HFX-90 spectrometer was used. All decoupling experiments were performed on the Bruker instrument.

solid and used for the determination of a proton nmr spectrum, which proved to be similar to the spectrum of the oxazinium ion **8**: multiplets at δ 2.15 (2 protons), 3.70 (2 protons), and 5.31 (1 proton), and singlets at δ 7.40 (5 protons) and 8.16 (4 protons). The low-field multiplet was particularly distinctive for structure **9**, and clearly excludes structure **2**.

The formation of an oxazine derivative from an allylic amide has only one precedent to our knowledge. It has been shown[5] that the allylic amide **10** as well as the hydroxyamide **11** give the oxazine derivative **12**



upon acid-catalyzed cyclization. That example is also good support for our mechanism.[3]

Experimental Section

N-(*trans*-**Cinnamyl**)-*p*-**nitrobenzamide** (**1**).—Cinnamyl amine, bp 84–87° (1.75 mm), prepared by the procedure of Bottini, *et al.*,[6] was treated with fresh *p*-nitrobenzoyl chloride (0.205 mol, 1:1 ratio with the amine) in the presence of 10 ml of triethylamine with 25 ml of benzene as the solvent. After standing for 10 min, the light yellowish crystals were filtered and washed stepwise with benzene, water, 6 *M* HCl, and water. The amide remaining weighed 2.3 g (85%) and had mp 131–132° (lit.[2] mp 131–132°). The ir and nmr spectra were consistent with the assigned structure (**1**).

2-*p*-**Nitrophenyl-6-phenyl-5,6-dihydro-1,3-oxazinium Cation** (**8**).—Amide **1** readily formed **8** upon following the procedure[2] of stirring the amide with sulfuric acid. Alternately, solutions of **8** were formed by extraction of **1** from CCl_4 solution. By this method the CCl_4 solution of **1** is added dropwise to rapidly stirred H_2SO_4.

Some attempts to isolate the oxazine **9** from the sulfuric acid solution gave a product which initially had the proper melting point, but rapidly deteriorated to an insoluble, high-melting material which was not further characterized.[7] This deterioration is probably accelerated by traces of acidic or basic impurities.[7]

Registry No.—**1**, 34562-10-2; **2**, 34562-11-3; **8**, 34557-90-9; **9**, 34562-12-4; sulfuric acid, 7664-93-9.

Acknowledgments.—One of us (S. P. M.) acknowledges the assistance of Dr. M. T. Emerson in obtaining the decoupled nmr spectra and Mr. J. T. Carroll for assistance in preparing the cinnamyl amine. The University of Alabama Research Committee is acknowledged for general research support through Grant No. 562 to C. U. P.

(5) R. Grewe, H. Pohlmann, and M. Schnorr, *Chem. Ber.*, **84**, 527 (1951).
(6) A. T. Bottini, V. Dev, and J. Klinck, *Org. Syn.*, **43**, 6 (1963).
(7) Since both oxazolines and oxazines readily polymerize, the insoluble matter was probably polymeric; *e.g.*, D. A. Tomalia and D. P. Sheetz, *J. Polym. Sci., Part A*, **4**, 2253 (1966).

2-(*trans*-β-Styrylsulfonyl)- and 2-((*trans*-2-Phenylcyclopropyl)sulfonyl)thiophene

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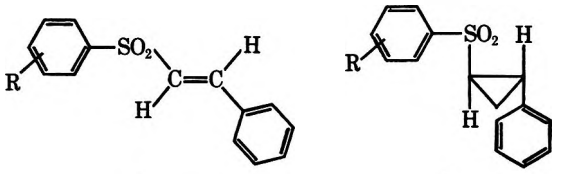
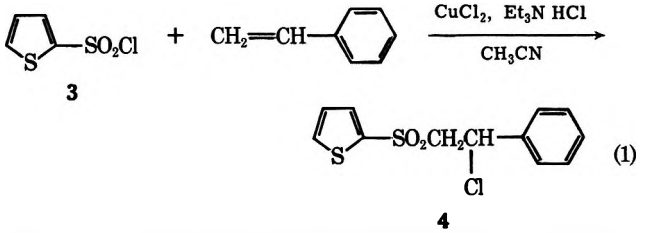
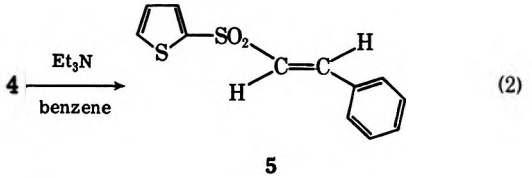
Although *trans*-1-phenyl-2-(arenesulfonyl)ethenes **1**[1,2] and *trans*-1-(arenesulfonyl)-2-phenylcyclopropanes **2**[3,4] are known, the corresponding heterocyclic analogs



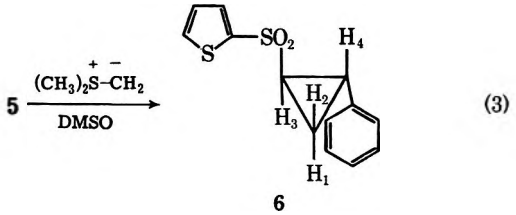
have not been reported. This note reports a facile synthesis of the 2-thiophene derivatives.

The copper-catalyzed addition of arenesulfonyl chlorides to styrenes[2] and other unsaturated substrates[5-7] has recently been described. In the present synthesis, the reaction of 2-thiophenesulfonyl chloride (**3**) with styrene in the presence of cupric chloride afforded 2-((β-chlorophenethyl)sulfonyl)thiophene (**4**, eq 1) in nearly quantitative yield. Subsequent treatment of **4** with triethylamine in benzene gave 2-(*trans*-β-styrylsulfonyl)thiophene (**5**, eq 2).[8] The reaction





of **5** with dimethylsulfonium methylide afforded 2-((*trans*-2-phenylcyclopropyl)sulfonyl)thiophene (**6**, eq 3) in 84% yield. The apparent first-order values for



(1) V. Baliah and M. Seshapathirao, *J. Org. Chem.*, **24**, 867 (1959).
(2) W. E Truce and C. T. Goralski, *ibid.*, **36**, 2536 (1971).
(3) W. E. Truce and V. V. Badiger, *ibid.*, **29**, 3277 (1964).
(4) W. E. Truce and C. T. Goralski, *ibid.*, **34**, 3324 (1969).
(5) M. Asscher and D. Vofsi, *J. Chem. Soc.*, 4962 (1964).
(6) W. E. Truce, C. T. Goralski, L. W. Christensen, and R. H. Bavry, *J Org. Chem.*, **35**, 4217 (1970).
(7) W. E. Truce and C. T. Goralski, *ibid.*, **35**, 4220 (1970).
(8) The vicinal coupling constant of the vinyl protons is 15.6 Hz, indicating that **5** has the trans configuration.

the vicinal coupling constants for the cyclopropyl ring protons of *cis*- and *trans*-1-(benzenesulfonyl)-2-phenylcyclopropane have been previously reported,[3] but no detailed analysis of the four spin cyclopropyl ring system was presented. In the present work, the chemical shifts and coupling constants of the cyclopropyl ring protons of **6** were determined from 60 and 100 MHz nmr spectra by iterative calculations using the program LAOCN3 (Table I). The values of the coupling constants definitely establish the configuration of **6** as trans.

TABLE I
NMR ($CDCl_3$) ASSIGNMENTS FOR THE CYCLOPROPYL RING PROTONS OF 6

	Chemical shift, δ[a]	Coupling constant, Hz
H_1	1.50	$J_{1,2} = -5.72$, $J_{1,3} = 8.35$, $J_{1,4} = 6.71$
H_2	1.89	$J_{2,3} = 5.40$, $J_{2,4} = 9.87$
H_3	2.77	$J_{3,4} = 4.44$
H_4	2.89	

[a] Recorded in parts per million downfield from tetramethylsilane.

Experimental Section[9]

2-((β-Chlorophenethyl)sulfonyl)thiophene (4).—In a 500-ml, three-neck flask equipped with a magnetic stirrer, a thermometer, a nitrogen inlet, and a reflux condenser fitted with a calcium chloride drying tube were placed 21.97 g (0.12 mol) of 2-thiophenesulfonyl chloride, 12.50 g (0.12 mol) of styrene, 0.16 g (1.2 mmol) of anhydrous cupric chloride, 0.25 g (1.8 mmol) of triethylamine hydrochloride, and 4.80 g of acetonitrile. The system was flushed with nitrogen, and the reaction mixture was heated at 95° for 2 hr. The reaction mixture was diluted with methanol (40 ml), and a crystalline solid formed immediately. The solid was filtered off, washed with water, and vacuum dried to give 32.40 g (93% yield) of crude sulfone as a slightly yellow solid, mp 90–92°. The crude sulfone was recrystallized from 180 ml of methanol to give 22.28 g of 2-((β-chlorophenethyl)sulfonyl)thiophene as small white needles, mp 92–93°. A 7.9-g second crop was also obtained.

Anal. Calcd for $C_{12}H_{11}ClO_2S_2$: C, 50.25; H, 3.87; Cl, 12.36; S, 22.36. Found: C, 50.31; H, 3.78; Cl, 12.40; S, 22.72.

2-(*trans*-β-Styrylsulfonyl)thiophene (5).—In a set-up as described above were placed 14.30 g (0.05 mol) of **4** and 300 ml of benzene. The system was swept with nitrogen. To the benzene solution, 7.50 g (0.075 mol) of triethylamine were added dropwise, with stirring. The reaction mixture was allowed to stir for 15 min and then filtered to remove the triethylamine hydrochloride which precipitated. The triethylamine hydrochloride was washed with several portions of benzene. The benzene was removed *in vacuo* from the combined filtrates, leaving a pale yellow solid. The solid was recrystallized from approximately 100 ml of absolute ethanol to give 10.09 g (81% yield) of 2-(*trans*-β-styrylsulfonyl)thiophene as small, slightly yellow needles, mp 97–99°.

Anal. Calcd for $C_{12}H_{10}O_2S_2$: C, 57.57; H, 5.03; S, 25.60. Found: C, 57.97; H, 5.09; S, 25.65.

2-((*trans*-2-Phenylcyclopropyl)sulfonyl)thiophene (6).—In the usual set-up were placed 3.28 g (0.013 mol) of **5**, 4.00 g (0.019 mol) of trimethylsulfonium iodide, and 75 ml of dimethyl sulfoxide. The system was swept with nitrogen. To this solution, a solution of 2.20 g (0.019 mol) of potassium *tert*-butoxide in 25 ml of dimethyl sulfoxide was added dropwise, with stirring. After the addition was complete, the reaction mixture was allowed to stir for 0.5 hr, and then diluted to approximately 700 ml with water. A white solid separated which was filtered off, air dried, and recrystallized from 50 ml of 95% ethanol to give 2.89 g (84% yield) of 2-((*trans*-2-phenylcyclopropyl)sulfonyl)thiophene, mp 116–118°.

Anal. Calcd for $C_{13}H_{12}O_2S_2$: C, 59.06; H, 4.58; S, 24.26. Found: C, 58.89; H, 4.70, S, 24.34.

(9) All melting points are uncorrected. The nmr spectral data were recorded on a Varian HA-100 spectrometer with tetramethylsilane as an internal standard. The microanalyses were performed by the Dow Analytical Laboratory.

Registry No.—**4**, 34566-07-9; **5**, 34566-08-0; **6**, 34566-09-1.

Acknowledgment.—The author wishes to thank Dr. Thomas E. Evans of the Dow Analytical Laboratory for obtaining and interpreting the nmr spectra.

Intermolecular Exchange in Methylphosphonic Difluoride–Amine Complexes *via* a Fluorine Bridged Dimer

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A few fluorophosphoranes, *e.g.*, $(CH_3)_3PF_2$ and $(CH_3)_2PF_3$, have recently been shown to undergo a temperature and concentration dependent intermolecular exchange *via* a fluorine bridged dimer.[1,2] Earlier, a similar process had been postulated to explain the exchange in, *e.g.*, SF_4, ClF_3, and BrF_3.[3] The purpose of this note is to report evidence which appears to support not only the formation of a labile complex between methylphosphonic difluoride (I) and amines, but also intermolecular exchange of fluorines in the complex *via* an analogous process.

Results and Discussion

The normal proton spectrum of I in benzene shows a doublet of triplets ($J_{P-H} = 19.3$, $J_{F-H} = 6.1$ Hz). When triethylamine is added to I, the doublet of triplets collapses to a doublet and the J_{P-H} value remains unchanged at 19.3 Hz regardless of amine concentration. The interaction of I and several secondary and tertiary amines was studied by measuring the pmr peak width at half-height of the methyl resonance of the protons on I. The extent of the amine interaction with I was dependent upon amine basicity and, to some extent, on the size of the alkyl or aryl groups on the amine nitrogen (Figure 1). Decoupling the fluorine nuclei of I resulted in the collapse of the pmr spectrum to a doublet similar in peak width to that caused by the more basic amines used in the investigation. The ability of primary amines to collapse the pmr spectrum of I could not be studied, since amide formation was quite rapid under our experimental conditions.

The normal ^{19}F nmr spectrum of I in benzene at 25° shows a doublet, each peak of which is split into a quartet by the methyl protons ($J_{P-F} = 1102$, $J_{F-H} = 6.1$ Hz). Upon the addition of small quantities of triethylamine (100:1, mole ratio of I to amine), the splitting of

(1) T. A. Furtsch, D. S. Dierdorf, and A. H. Cowley, *J. Amer. Chem. Soc.*, **92**, 5759 (1970).
(2) H. Dreeskamp and K. Hildenbrand, *Z. Naturforsch. B.*, **26**, 269 (1971).
(3) E. L. Muetterties and W. D. Phillips, *J. Amer. Chem. Soc.*, **79**, 322 (1957); **81**, 1084 (1959).

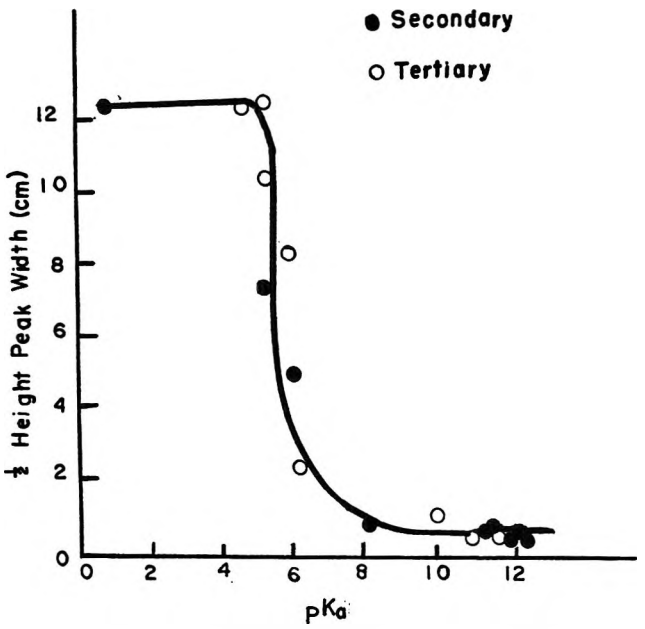


Figure 1.—The effect of amine basicity on the pmr spectral collapse in benzene solution of the methyl protons of methylphosphonic difluoride: methylphosphonic difluoride 2.2 × 10^{-3} mol, all amines 5.5 × 10^{-4} mol, 0.5 ml of benzene.

the doublet by the methyl protons was no longer apparent and the doublet had a smaller J_{P-F} value. Further additions of triethylamine caused the J_{P-F} value to decrease until a 1:1 molar ratio of I to triethylamine was reached; the spectrum then showed a single resonance.

The ^{31}P nmr spectrum of I shows a triplet, each peak of which is split into a quartet. On the addition of small quantities of triethylamine (100:1, mole ratio of I to amine), only a very broad signal could be observed. Cooling this same sample to −20° caused the slight reappearance of the triplet. An attempt was made to observe this temperature dependence in the pmr spectrum.

Raising the temperature of a 50:1 molar ratio of I and triethylamine from 33 to 100° caused no change in the J_{P-H} value; no line broadening was observed. Since the proton and ^{19}F spectra of I were only partially collapsed by the interaction of I with 4-phenylpyridine, the effect of temperature on the interaction of I and this amine was investigated. Raising the temperature from 10 to 73° of a benzene solution containing 0.006 mol of I and 0.001 mol of 4-phenylpyridine resulted in an increased collapse of the methyl resonance. However, the doublet of triplets was still in evidence, and the J_{P-H} value remained constant at 19.3 Hz. A similar temperature change had no effect on the proton spectrum of I in the absence of amine.

The spectral changes observed are consistent with an exchange phenomenon which is dependent upon amine basicity and also suggest a slight temperature dependence for the interaction. The loss of P–F coupling in the amine complex while the P–H coupling remains intact suggests that P–F bonds are broken in the exchange process. A similar loss of P–F coupling with retention of the P–H coupling has also been observed in the exchange of fluorines in $(CH_3)_3PF_2$.[1]

To test the possibility that the exchange in the amine complex was a heterolytic P–F bond cleavage, we attempted to trap exchanging fluoride anions. The ^{19}F nmr spectrum of I (0.004 mol) and triethylamine (0.004 mol) in benzene (0.5 ml) was taken to ensure that collapse had occurred. Triethylammonium tosylate (0.001 mol) was added and the ^{19}F spectrum was observed for 24 hr to ascertain if triethylammonium fluoride (II) was being produced by reaction 1. No evi-

$$\underset{\text{I}}{CH_3POF_2} + Et_3NH^+OTs^- \overset{Et_3N:}{\rightleftharpoons} \underset{\text{II}}{Et_3NH^+F^-} + CH_3POFOTs \quad (1)$$

dence for the formation of II was observed. Furthermore, no evidence for the formation of IV (eq 2) was

$$\underset{\text{I}}{CH_3POF_2} + \underset{\text{III}}{CH_3POCl_2} \overset{Et_3N:}{\rightleftharpoons} \underset{\text{IV}}{2CH_3POFCl} \quad (2)$$

obtained when an equimolar mixture of I and III was allowed to react in the presence of triethylamine, even when the concentration of the amine was four times that of I.[4]

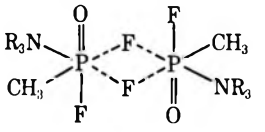
An attempt was also made to observe amide formation from I, and 12 different secondary amines under conditions where collapse of the methyl resonance in the pmr spectrum was observed. There was no evidence of amide formation.

Several reports have indicated that dissociation into ions does not take place when some phosphorus V fluorides are complexed with amines.[5,6] In our studies, if heterolytic P–F bond cleavage were responsible for the observed spectral changes, then one would expect to see some evidence for it through amide formation or the formation of II. In addition to these data, we have observed that fluoride ion will displace chloride ion from III when NaF is added to a solution of III in DMF. Consequently, if heterolytic P–F bond cleavage were taking place, one would also expect to see some evidence for it in the formation of IV. Furthermore, no collapse of the pmr spectrum is observed when methylphosphonothioic difluoride (V) is mixed with amines under our experimental conditions. However, upon addition of excess I to the above, collapse of both I and V can be observed in the pmr spectrum (eq 3 and 4). These

$$\underset{\text{V}}{CH_3PSF_2} + \text{Amine} \longrightarrow \text{No apparent effect} \quad (3)$$

$$\underset{\text{V}}{CH_3PSF_2} + \underset{\text{I}}{CH_3POF_2} + \text{Amine} \longrightarrow \text{Collapse of both difluorides} \quad (4)$$

data, in conjunction with the loss of P–F coupling while the P–H coupling remains intact, suggest that the transition state for the exchange in the amine complex with I is similar to the bridged species VI shown below.



VI

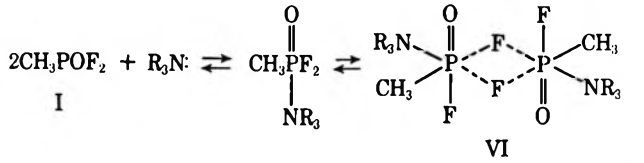
(4) An equimolar mixture of pure methylphosphonic difluoride and methylphosphonic dichloride was observed for 7 days at room temperature. No evidence for halide exchange was observed. B. M. Zeffert, P. B. Coulter, and H. Tannenbaum, *ibid.*, **82**, 3843 (1960).

(5) F. N. Teble and E. L. Muetterties, *Inorg. Chem.*, **6**, 129 (1967).

(6) L. Lunazzi and S. Brownstein, *J. Magn. Resonance*, **1**, 119 (1969).

The lack of formation of IV in eq 2 and the stability of IV to reaction conditions may simply indicate that the mixed bridge is relatively unstable.[7] Some additional support for this view comes from the inability of chloride ion to readily displace fluoride ion from I in the presence of amine under our reaction conditions.

Our data support a labile complex between I and amines and also an exchange phenomenon; however, it does not appear that the complex is undergoing an intramolecular exchange. The results of our work seem to be best explained by rapid intermolecular exchange of fluorine *via* the fluorine bridged dimer shown in eq 5.



(5)

Experimental Section

Materials.—Methylphosphonic dichloride[8] and methylphosphonic difluoride[9] were prepared, distilled, and stored under dry nitrogen. The methylphosphonothioic difluoride was obtained from Ash-Stevens, Inc., under Contract No. DAAA15-69-C-0584. All amines were obtained from commercial sources and dried over CaO before use. Thiophene-free benzene from Mallinckrodt Chemical Works was distilled and dried over molecular seives.

Triethylammonium tosylate was prepared by adding triethylamine (0.1 mol) to toluenesulfonic acid (0.1 mol) dissolved in 50 ml of benzene. The solution was dried over anhydrous $MgSO_4$ and decanted into a dry flask, and the solvent was removed. The nmr spectrum of the solid which remained indicated that it was the desired tosylate. The compound was used without further purification.

Instruments.—The proton nmr spectra were recorded at 60 MHz using a Varian A-60D nmr spectrometer. The ^{19}F and ^{31}P studies were carried out at 94.1 and 40.5 MHz, respectively, using a Varian HA-100 nmr spectrometer. These spectra were obtained in the unlocked (HR) mode using the V-3507 unit to sweep the field.

Registry No.—I, 22382-13-4.

(7) Methylphosphonic chlorofluoride (IV) is stable to our reaction conditions.

(8) A. M. Kinnear and E. A. Perren, *J. Chem. Soc.*, 3437 (1952).

(9) T. P. Dawson and K. C. Kennard, *J. Org. Chem.*, **22**, 1671 (1957).

Radiation-Induced and Electrochemical Formation of 3-Substituted 4,4-Dimethyl-γ-butyrolactone from α,β-Unsaturated Ester

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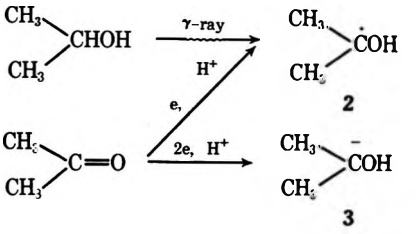
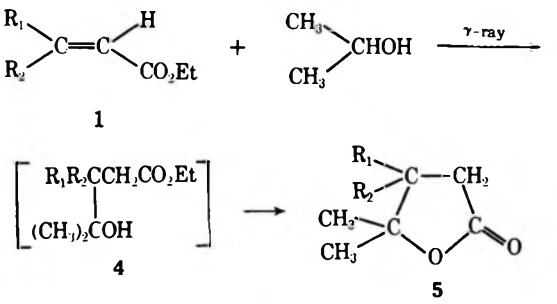
It has been previously reported[1] that radiation and ultraviolet-induced addition reactions of various alcohols to ethyl crotonate gave the corresponding 3-methyl-4-alkyl-substituted γ-butyrolactones. In the present paper, the radiation-induced addition reactions of 2-propanol and electrochemical reductive addition reactions of acetone to α,β-unsaturated esters are reported.

Since it is known that radiolysis of 2-propanol produces α-hydroxy radical 2,[2-4] and electroreduction of acetone in a protic solvent gives radical 2 or anion 3,[5-8] both addition reactions are expected to give the



identical products. In the present work, it was found that substituted γ-butyrolactones were obtained in fairly good yields by using such simple procedures.

Irradiation of α,β-unsaturated ester **1a–e** in a tenfold excess of 2-propanol with ^{60}Co γ-rays gave the corresponding 3-substituted 4,4-dimethyl-γ-butyrolactone **5a–e**.



a, $R_1 = R_2 = H$ **d**, $R_1 = H$; $R_2 = CO_2Et$
b, $R_1 = CH_3$; $R_2 = H$ **e**, $R_1 = CO_2Et$; $R_2 = H$
c, $R_1 = R_2 = CH_3$ **f**, $R_1 = C_6H_5$; $R_2 = H$

The yield of lactones, conversion of α,β-unsaturated esters, and G values of lactone formation and ester consumption are listed in Table I. G values were calculated from the low-conversion linear part of the curve which was obtained from the plot of the yield of lactone and the conversion of ester against the irradiation time.

Ethyl acrylate (**1a**) produced no lactone, probably because it easily polymerized by radical initiation. This is indicated by its high value of $G(-\mathbf{1a})$.

Reactivity of the α,β-unsaturated ester toward the intermediate radical **6** seems to control the yield of lactone. A reactive ester such as **1a** proceeds predominantly in eq 2 to give a polymer, but in a less reactive ester an intermediate radical **6** may preferentially

(1) M. Tokuda, Y. Yokoyama, T. Taguchi, A. Suzuki, and M. Itoh, *J. Org. Chem.*, in press.

(2) W. R. McDonell and A. S. Newton, *J. Amer. Chem. Soc.*, **76**, 4651 (1954).

(3) (a) K. Hirota and M. Hatada, *Bull. Chem. Soc. Jap.*, **34**, 1644 (1961); (b) M. Hatada and K. Hirota, *ibid.*, **38**, 26 (1965).

(4) H. Muramatsu, K. Inukai, and T. Ueda, *ibid.*, **40**, 903 (1967), and references cited therein.

(5) F. D. Popp and H. P. Schultz, *Chem. Rev.*, **62**, 19 (1962).

(6) (a) T. Sekine, A. Yamura, and K. Sugino, *J. Electrochem. Soc.*, **112**, 439 (1965); (b) A. Yamura, T. Sekine, and K. Sugino, *J. Electrochem. Soc. Jap.*, **34**, 110 (1936).

(7) K. Sugino and T. Nonaka, *J. Electrochem. Soc.*, **112**, 1241 (1965).

(8) K. Sugino and T. Nonaka, *Electrochim. Acta*, **13**, 613 (1968).

TABLE I
RADIATION-INDUCED ADDITION REACTION OF 2-PROPANOL TO α,β-UNSATURATED ESTER[a]

Compd	Yield of lactone 5, %[b]	G(5)	Conversion of ester 1, %[b]	G(−1)
1a	0	0	100	100
1b	44	8	86	19
c	41			
1c	29	5	64	10
1d	70	22	98	36
d	69			
1e	22	11	94	66
1f	0	0	35	4

[a] Irradiation time, 72 hr; dose rate, 8×10^5 r/hr; mole ratio of 2-propanol to ester, 10. [b] Based on α,β-unsaturated esters employed. [c] Instead of ethyl crotonate, crotonic acid was used. [d] Instead of ethyl maleate, maleic acid was used.

sults in the larger value of $G(-1)$. On the other hand, diethyl maleate would be mostly consumed in eq 3, resulting in the larger value of $G(5)$.

Irradiation of α,β-unsaturated acid, such as crotonic acid and maleic acid, produced γ-butyrolactone in almost the same yield as the corresponding esters.

When a mixture of α,β-unsaturated ester **1**, acetone, 20% sulfuric acid, and water was electrolyzed for 1 hr with a terminal voltage of 75–95 V, Michael-type addition of anion **3** to α,β-unsaturated ester occurred to give γ-lactone through the intermediate ester **4**. The

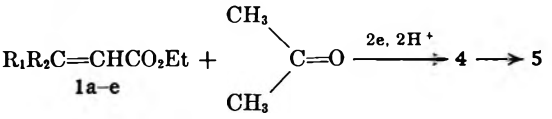


TABLE II
ELECTROCHEMICAL ADDITION REACTION OF ACETONE TO α,β-UNSATURATED ESTER[a]

Compd	Substrate: Ester, g	Acetone, ml	20% H_2SO_4, ml	H_2O, ml	Terminal voltage, V	Current, A	Yield of lactone 5, %[b]	Conversion of ester 1, %[b]
1a	1.0	20	0.83	2	90	0.9	95	100
1b	1.0	20	0.83	2	90	0.9	30	60
c	1.0	20	0.83	5	80	1.3	36	
1c	1.0	20	0.83	2	93	0.8	Trace	30
1d	1.0	20	0.83	0	85	1.0	59	100
	1.0	20	0.83	5	80	1.2	Trace[d]	100
1e	1.0	20	3.30	0	75	1.5–2.0	21	100
	1.0	20	0.83	5	80	1.3	8[e]	100
1f	1.0	20	1.66	0	83	1.0	0	

[a] Electrolysis was conducted under the above conditions for 1 hr. [b] Based upon ester employed. [c] Instead of ester, crotonic acid was used. [d] Diethyl succinate was produced in 95% yield. [e] Diethyl succinate was produced in 90% yield.

abstract a hydrogen from 2-propanol to form the γ-hydroxy ester **4** (eq 3). The interesting result is that

$$\underset{\mathbf{1}}{R_1R_2C{=}CHCO_2Et} + \underset{\mathbf{2}}{(CH_3)_2\dot{C}OH} \longrightarrow \underset{\mathbf{6}}{R_1R_2C(\dot{C}HCO_2Et)(CH_3)_2COH} \quad (1)$$

$$\mathbf{6} + n\underset{\mathbf{1}}{R_1R_2C{=}CHCO_2Et} \longrightarrow \text{telomer, polymer} \quad (2)$$

$$\mathbf{6} + (CH_3)_2CHOH \longrightarrow \mathbf{4} + \mathbf{2} \quad (3)$$

the G value of lactone formation was larger in diethyl maleate (**1d**) than the corresponding fumarate (**1e**) but the G value of ester consumption was about two times larger for diethyl fumarate. This is probably the result of trans olefin being more reactive towards radical addition than the cis isomer.[9] In support of this, Szwarc, *et al.*, report that the rate of methyl radical addition to diethyl fumarate is about six times faster than to diethyl maleate.[10] Also, the yield of 1:1 adduct in the radiation-induced addition of butyraldehyde to diethyl maleate is about three times larger than that to diethyl fumarate.[11] Since diethyl fumarate is more reactive toward radical addition, it would be consumed mainly in radical chain polymerization (eq 2), which re-

(9) W. A. Pryor, "Free Radical", McGraw-Hill, New York, N. Y., 1966, p 223

(10) (a) A. R. Barder, R. P. Buckly, F. Leavitt, and M. Szwarc, *J. Amer. Chem. Soc.*, **79**, 5621 (1957); (b) M. Szwarc and J. H. Binks in "Theoretical Organic Chemistry, The Kekule Symposium," Butterworths, London, 1958, p 278.

(11) R. H. Wiley and J. R. Harrell, *J. Org. Chem.*, **25**, 903 (1960).

electrode employed was a mercury pool (cathode) and a platinum plate (anode), and the procedure for electrolysis was simplified with no partition between the cathode and the anode chamber. The yield of lactone **5**, the conversion of ester **1**, and its reaction conditions are summarized in Table II.

The remarkable difference between the radiation-induced and the electrochemical addition reactions was that in the latter case 4,4-dimethyl-γ-butyrolactone (**5a**) was obtained in an almost quantitative yield. From this result, it is suggested that the reactive species in the electrolysis is not a radical **2** but an anion **3**, as Sugino, *et al.*,[8] have already pointed out. The yield of lactone is gradually decreased as alkyl substitution at the β position of α,β-unsaturated ester increases.

In the case of diethyl maleate (**1d**) and diethyl fumarate (**1e**), ethyl 2,2-dimethylparaconate (**5d**) was obtained in yields of 59 and 21%, respectively, but in some conditions an electrolytic reduction of ester took place to produce diethyl succinate.

Experimental Section

Gas–liquid chromatographic analyses were carried out with a Yanagimoto Model GCG-550 and preparative work was done with a Varian Autoprep 700. Infrared spectra were obtained with a Hitachi EPI-G22, and nuclear magnetic resonance spectra were measured with a JEOL 3H-60 (tetramethylsilane as the internal standard). Mass spectra were obtained with a Hitachi RMU-6E. Quantitative glpc analyses were carried out by an

internal standard method. All melting points and boiling points are uncorrected.

All reagents were distilled or recrystallized before use. Ethyl crotonate, ethyl β,β-dimethylacrylate, diethyl maleate, diethyl fumarate, and ethyl cinnamate were prepared by esterification of the corresponding acids. β,β-Dimethylacrylic acid was prepared by the procedure reported by Smith, *et al.*[12] 2-Propanol was dried over calcium oxide and acetone was distilled in the presence of magnesium. Mercury was purified with dilute nitric acid.

General Procedure for Radiation-Induced Reaction.—The general procedure was carried out by the method previously reported.[1] For glpc analyses, a 15% FFAP (Free Fatty Acid Polyester) column coated on Diasolid M (Nihon Chromato Work, Ltd.) and a 15% Apieson Grease L column coated on Diasolid L were used at 150–240° with 4-*tert*-butyltoluene and diethyl phthalate as the internal standard.

General Procedure for Electrochemical Reaction.—The electrochemical cell used was a cylindrical vessel, 3 cm in diameter and 15 cm in height, with no partition between the cathode and the anode chamber. The reaction vessel was cooled with running water throughout the electrolysis. The mercury pool (55 g) at the bottom of the cell was used as the cathode. The anode was a platinum plate (1 × 1 cm²), which was held 1 cm apart from the mercury electrode.

A typical procedure is as follows: a mixture of α,β-unsaturated ester (1 g), acetone (20 ml), 20% sulfuric acid (0.8–3.3 ml), and water (0–5 ml) was electrolyzed for 1 hr with a terminal voltage of 75–95 V at a current of 0.35–1.6 A, and then the resultant mixture was neutralized with a 5% NaOH solution and extracted with ether. The ether solution was analyzed by glpc.

Analysis of Products.—A product was separated by a distillation and a preparative glpc (silicone gum rubber SE-30 or Apieson Grease L), and identified from ir, nmr and mass spectral data. Physical properties are summarized in Table III.

TABLE III

PROPERTIES OF γ-BUTYROLACTONES

Compd	Bp, °C (mm)	n_D (°C)	Found, % C	Found, % H	Calcd, % C	Calcd, % H
5a	110.5–111.5 (45)[a]	1.4352 (15)[b]	62.95	8.79	63.13	8.83
5b	97 (15)[c]	1.4373 (20)[d]	65.32	9.48	65.59	9.44
5c	100–103 (17) mp 100–101.5[e]		67.30	9.85	67.57	9.93
5d	138–140 (8)	1.4445 (25)	58.26	7.71	58.05	7.58
f	mp 174–175[g]		53.05	6.35	53.16	6.37

[a] Lit. bp 201–206° (760 mm): R. T. Arnold, J. S. Buckley, Jr., and J. Richter, *J. Amer. Chem. Soc.*, **69**, 2322 (1947). Lit. bp 89–91° (17 mm): R. L. Frank, R. Armstrong, J. Kwiatek, and H. A. Price, *ibid.*, **70**, 1379 (1948). [b] Lit. n_D 1.4352 (20°): *ibid.*, **70**, 1379 (1948). [c] Lit. bp 216–217° (744 mm): J. W. Huffman and J. W. Bethea, *J. Org. Chem.*, **30**, 2956 (1965). [d] Lit. n_D 1.4402 (17°): M. Pfau, R. Dulou, and M. Vilkas, *C. R. Acad. Sci.*, **251**, 2188 (1960). [e] Lit. mp 99–100°: A. W. Burgstahler and D. E. Wetmore, *J. Org. Chem.*, **26**, 3516 (1961). [f] 2,2-Dimethylparaconic acid. [g] Lit. mp 176°: G. O. Schenck, G. Koltzenburg, and H. Grossmann, *Angew. Chem.*, **69**, 177 (1957). Lit. mp 174°: J. F. Laporte and R. Rambaud, *C. R Acad. Sci., Ser. C*, **262**, 1095 (1966).

Registry No.—**1a**, 140-88-5; **1b**, 623-70-1; **1c**, 638-10-8; **1d**, 141-05-9; **1e**, 623-91-6; **1f**, 4192-77-2; **5a**, 3123-97-5; **5b**, 2981-96-6; **5c**, 16466-24-3; **5d**, 34566-25-1; 2-propanol, 67-63-0; 2,2-dimethylparaconic acid, 79-91-4.

(12) L. I. Smith, W. W. Prichard, and L. J. Spillane, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 302.

The Synthesis of 2,2,5-Trimethyl-6-hydroxy-2*H*-naphtho[1,2-*b*]pyran and 2-(γ,γ-Dimethylallyl)-3-methylnaphthoquinone. A New Route to Naphthopyrans and the Vitamin K_1 Series

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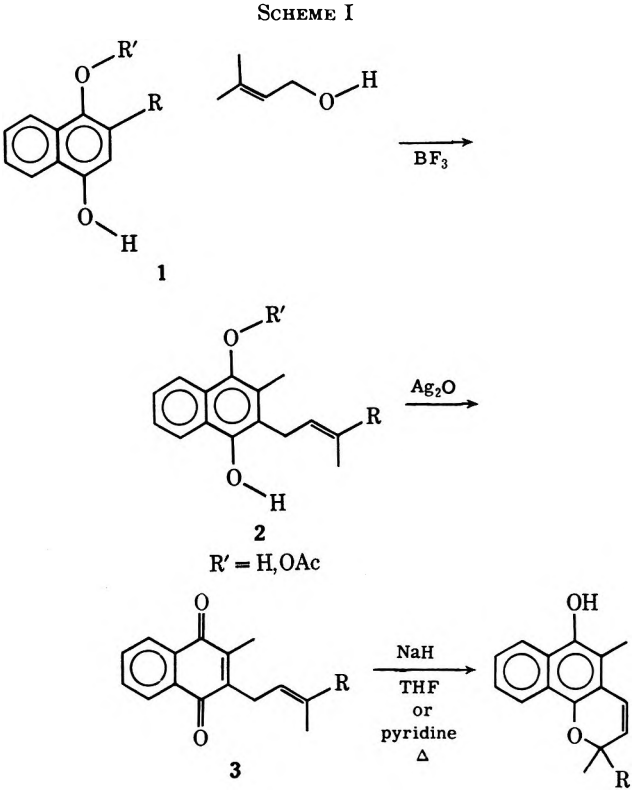
Received May 10, 1971

In connection with an investigation of possible intermediates in oxidative phosphorylation, a moderately large quantity of the naphthopyranol **11** and its acetate ester **8** and methyl ether **10** derivatives were desired. A literature search divulged no specific preparations of these compounds but did suggest several possible general approaches. Alkylation of menadiol or of menadiol-1-acetate (**1**) by allylic alcohols, catalyzed by boron trifluoride,[1] affords intermediates **2** which can be oxidized to quinones **3** and then cyclized to the desired naphthopyranol system by sodium hydride–THF[2] or pyridine[3] (Scheme I). These alkylations suffer, however, from the necessity of using large excesses of **1** to achieve good yields. Yields in the alkylation step are typically 20–40%[4] and conversions range from minute to about 20%. Although the oxidation step is quite efficient, yields in the subsequent cyclization are not

SCHEME I



(1) R. Hirschmann, R. Miller, and N. L. Wendler, *J. Amer. Chem. Soc.*, **76**, 4592 (1954).

(2) A. Wagner, D. Wittreich, B. Arison, N. Trenner, and K. Folkers, *ibid.*, **85**, 1178 (1963).

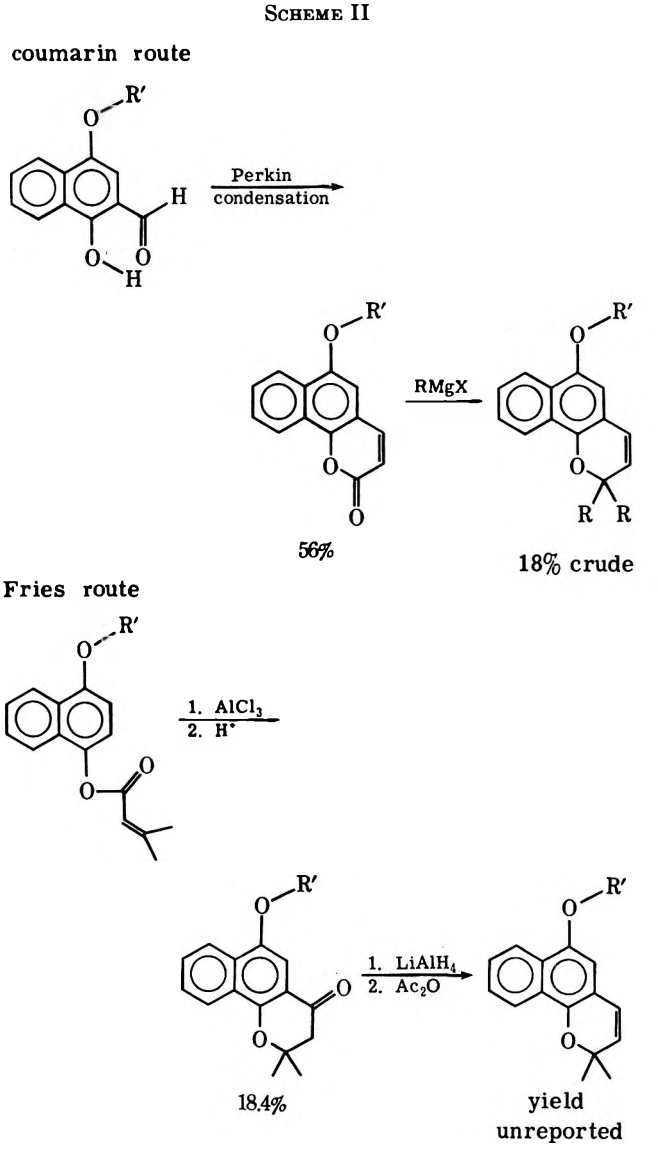
(3) D. McHale and J. Green, *Chem. Ind. (London)*, 1867 (1962).

(4) (a) C. C. Lee, F. C. G. Hoskin, L. W. Trevoy, L. B. Jaques, and J. W. Spinks, *Can. J. Chem.*, **31**, 769 (1953); (b) O. Isler and K. Doebel, *Helv. Chim. Acta*, **27**, 225 (1954).

outstanding (45% is the maximum isolated yield reported). In addition, column chromatography is generally required in the first and last steps, and finally, the resultant pyranol has not been isolated as such but is trapped as an acetate or phosphate ester. Because of these considerations and also because initial results using this approach were disappointing, a more efficient synthetic route to the pyranol **11** and its derivatives was sought.

Two other potential approaches are embodied in syntheses of lapachenole (Schme II).[5] The coumarin

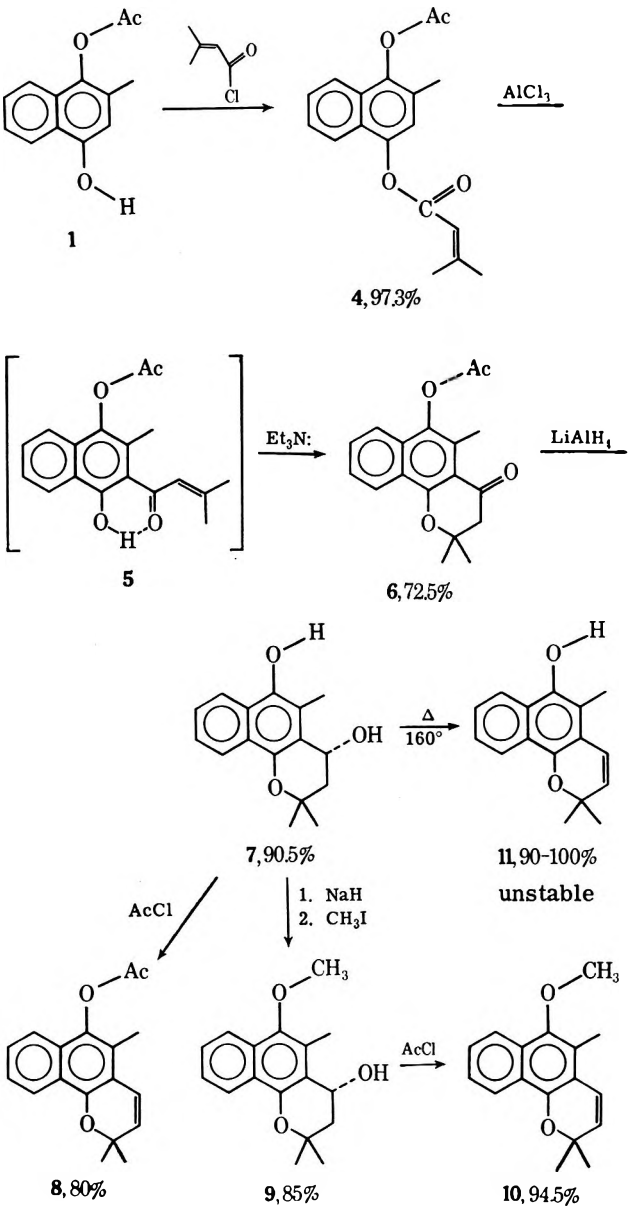
SCHEME II



route lacks appeal because of nonregiospecificity in the Grignard step. The Fries route has no obvious flaws, but the reported yields are poor. Nevertheless, this route appeared to have promise and was investigated. The analogous series of reactions illustrated in Scheme III can now be recommended as affording the desired naphthopyranyl compounds in good yield (51–64%). Five steps (six for the ether **9**), instead of the three used in the conventional procedure, are required. However, the yields in each step are high with the new route, at least in the present instances, and one of the steps requires no purification procedure. The other steps in-

(5) R. Livingstone and R. B. Watson, *J. Chem. Soc.*, 3701 (1956).

SCHEME III



volve purification by recrystallization. The new method thus may have some distinct advantages and it is hoped that it will prove equally applicable to the syntheses of higher isoprenologs of the 2*H*-naphtho[1,2-*b*]pyran system.

Reduction of the readily isolated Fries product **5** by lithium aluminum hydride gives 2-(γ,γ-dimethylallyl)-3-methylnaphthoquinone[6] in 36% yield, thus providing another potential route of entry into the vitamin K_1 series. Use of lithium aluminum deuteride gives specifically methylene dideuterated quinone. No attempts were made to optimize the yield, so it is quite possible that the 36% yield can be considerably improved. However, at this point the method appears somewhat inferior to the conventional Friedel–Crafts alkylation approach.[4]

Experimental Section

Melting points were determined without correction, using a Mel-Temp apparatus. Infrared spectral measurements utilized

(6) R. Mamont, R. Cohen, R. Azerad, and M. Vilkas, *Bull. Soc. Chim. Fr.*, 2513 (1965).

a Beckman IR-5, nmr spectra a Varian A-60, spectrometer unless otherwise noted. A consolidated Electrodynamics 21-102 spectrometer was used for obtaining mass spectra.

4-Acetoxy-3-methyl-1-naphthyl-β,β-dimethyl Acrylate (4).—A stirring solution of 26.05 g (0.12 mol) of menadiol-1-acetate[7] and 17.2 g (0.145 mol) of β,β-dimethylacryloyl chloride[8] in 200 ml of chloroform was refluxed for 2.5 hr under nitrogen and cooled to 25°, followed by addition of 200 ml of water. The customary work-up afforded a viscous oil. Crystallization from hexane gave 35.0 g (97.3%) of **4** as white crystals: mp 101–103°; ir ($CHCl_3$) ν 1755, 1735 cm^{-1}; nmr ($CDCl_3$) τ 8.02 (d, 3 H, J = 1.2 Hz), 7.77 (d, 3 H, J = 1.0 Hz), 7.72 (s, 3 H), 7.61 (s, 3 H), 3.93 (m, 1 H), 2.86 (broad s, 1 H), and 2.34 (m, 4 H). Two recrystallizations from ether increased the melting point to 103–104.5°.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.59; H, 6.26.

3-(3-Methyl-2-butenoyl)-4-hydroxy-2-methyl-1-naphthyl Acetate (5).—To a mechanically stirred suspension of aluminum chloride (14.3 g, 0.107 mol, 4 equiv) in 100 ml of methylene chloride was added, over a 10-min period, a solution of 8.0 g (0.0268 mol) of **4** in 50 ml of methylene chloride. The reaction was monitored by ir and continued until, after about 2.0 hr, the 1735-cm^{-1} absorption was replaced by the 1635-cm^{-1} absorption of the enol. Only a small amount of the cyclized ketone **6** was detectable by a peak at 1685 cm^{-1}. The reaction mixture was then poured onto a mixture of 600 g of ice and 100 ml of hydrochloric acid, stirred for 15 min, and separated. The aqueous layer was extracted four times with 100-ml portions of methylene chloride and the combined organic phases were worked up in the usual way. There was obtained 8.28 g of crude **5** as an orange gum: ir ($CHCl_3$) ν 1755, 1635 cm^{-1}; nmr ($CDCl_3$) τ 8.04 (d, 3 H, J = 1.25 Hz), 7.83 (d, 3 H, J = 1.0 Hz), 7.65 (s, 3 H), 7.58 (s, 3 H), 4.45 (m, 1 H), 2.5 (m, 3 H), 1.53 (m, 1 H), and −3.08 (s, 1 H). Purification of this intermediate was not attempted in view of its facile cyclization.

6-Acetoxy-3,4-dihydro-2,2,5-trimethyl-2*H*-naphtho[1,2-*b*]pyran-4-one (6).—A solution of 35.0 g (0.117 mol) of crude **5** in 100 ml of benzene containing 19.7 ml (0.141 mol) of triethylamine was stirred for 12 hr at room temperature. Evaporation of the solvent and recrystallization from hexane gave 25.3 g (72.5%, based on **4**) of **6**. Two further recrystallizations from ether afforded 16.2 g of **6** as yellow crystals: mp 142–143°; ir (CS_2, IR-7) ν 1765, 1683 cm^{-1}; nmr ($CDCl_3$) τ 8.49 (s, 6 H), 7.59 (s, 3 H), 7.45 (s, 3 H), 7.24 (s, 2 H), 2.54 (m, 3 H) and 1.73 (m, 1 H); mass spectrum m/e 298 (M), 255.

Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.43; H, 5.87.

3,4-Dihydro-4,6-dihydroxy-2,2,5-trimethyl-2*H*-naphtho[1,2-*b*]pyran (7).—A solution of 8.0 g (0.0268 mol) of **6** in 400 ml of ether was added gradually to a suspension of 4.8 g (0.126 mol) of lithium aluminum hydride in 200 ml of ether. After a 6-hr period the excess hydride was destroyed by slow addition of 10 ml of 95% ethanol and then by addition of water until bubbling ceased. The ethereal solution was decanted from the solids, the latter were leached with ether, and the combined ether phases were washed and evaporated. The solid residue was stirred with hexane, washed with hexane, and air dried, yielding 5.88 g (90.5%) of **7** as tan crystals, mp 153–155° dec. Two recrystallizations from acetone–carbon tetrachloride gave white crystals of **7**: mp 138–140°; ir (KBr, IR-7) ν 3410 cm^{-1} (s); nmr (10% DMSO-d_6–$CDCl_3$) τ 8.57 (s, 3 H), 8.53 (s, 3 H), 7.89 (d, 2 H), 7.54 (s, 3 H), 6.06 (d, 1 H), 5.08 (m, 1 H), 2.63 (m, 2 H), and 1.92 (m, 2 H); mass spectrum m/e 240 (M − H_2O).

Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.61; H, 7.11.

2,2,5-Trimethyl-2*H*-naphtho[1,2-*b*]pyranyl-6 Acetate (8).—A solution of 10.05 g (0.039 mol) of diol **7** in 50 ml of acetyl chloride was stirred for 25 min at room temperature and then concentrated to a dark solid. Benzene (75 ml) was added and the solution was refluxed for 12 hr, cooled, treated with Darco G-60, filtered through Super-Cel, and finally evaporated under reduced pressure. Crystallization from hexane afforded 9.15 g (80% yield) of **8** as tan crystals, mp 115–118°. Two recrystallizations from ether–hexane gave **8** as white crystals: mp 121.5–122.5°; ir ($CHCl_3$) ν 1750 cm^{-1}; nmr ($CDCl_3$) τ 8.54 (s, 6 H), 7.80 (s, 3 H), 7.63 (s, 3 H), 4.4, 3.48 (q, 2 H, J = 10.0 Hz), 2.54 (m, 3 H), and 1.84 (m, 1 H); mass spectrum m/e 282 (M).

Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.84; H, 6.55.

3,4-Dihydro-6-methoxy-2,2,5-trimethyl-2*H*-naphtho[1,2-*b*]pyran-4-ol (9).—To a cooled (5°) solution of 1.06 g (4.1 mmol) of **7** in 35 ml of DMF under nitrogen was added 0.21 g (4.6 mmol) of sodium hydride dispersion. The mixture was stirred for 10 min after the gas evolution subsided, followed by addition of 1.98 g (0.014 mol) of methyl iodide. After stirring for 0.5 hr the reaction mixture was poured into 200 ml of water and 100 ml of chloroform and worked up in the usual way. The product crystallized from hexane (0.912 g, 85% yield) as tan crystals: mp 127–129°; nmr (10% DMSO-d_6–$CDCl_3$) τ 8.57 (s, 3 H), 8.53 (s, 3 H), 7.92 (d, 2 H, J = 4.5 Hz), 7.52 (s, 3 H), 6.20 (s, 3 H), 5.1 (m, 1 H), 2.58 (m, 2 H), and 1.96 (m, 4 H); mass spectrum m/e 272 (M), 254, 239.

6-Methoxy-2,2,5-trimethyl-2*H*-naphtho[1,2-*b*]pyran (10).—A solution of 4.55 g (0.0167 mol) of **9** in 40 ml of acetyl chloride was stirred for 0.5 hr at room temperature. Concentration of the dark solution gave a solid to which was added 150 ml of benzene and the solution was refluxed for 12 hr. After cooling to 25°, the solution was diluted with 200 ml of water and worked up as usual. The resultant dark oil was chromatographed on 100 g of silica gel. The hexane eluates were combined and evaporated, affording 4.0 g (94.5%) of **10**, a viscous, yellow oil which crystallized upon standing: nmr ($CDCl_3$) τ 8.55 (s, 6 H), 7.63 (s, 3 H), 6.2 (s, 3 H), 4.48, 3.43 (q, 2 H, J = 10.0 Hz), 2.58 (m, 2 H), and 1.92 (m, 2 H); mass spectrum m/e 254 (M). An analytical sample was prepared by repeated chromatography on basic alumina (hexane).

Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.36; H, 7.07.

2,2,5-Trimethyl-2*H*-naphtho[1,2-*b*]pyran-6-ol (11).—A sample of 0.258 g (1.0 mmol) of the diol **7** was heated for 15 min at 160° under nitrogen and evaporated for 1 hr *in vacuo* at 50°, affording alcohol **11**: ir ($CHCl_3$) ν 3600, 3400 cm^{-1}; nmr (10% DMSO-d_6–$CDCl_3$) τ 8.62 (s, 6 H), 7.7 (s, 3 H), 4.46, 3.49 (q, 2 H, J = 10.0 Hz), 2.75 (m, 2 H), 2.52 (broad s, 1 H), and 1.99 (m, 2 H). Not appreciable amounts of impurities were noted in the nmr spectrum. Further attempts at purification resulted in oxidative decomposition of the pyranol **11**.

2-(γ,γ-Dimethylallyl)-3-methyl-1,4-naphthoquinone (3).—A solution of 8.0 g (26.8 mmol) of enol **5** dissolved in 100 ml of anhydrous ether was added slowly to 8.0 g (0.211 mol) of lithium aluminum hydride suspended in 150 ml of ether. The mixture was stirred overnight at room temperature, the excess hydride was decomposed with a minimum amount of water, and the ether supernatant was worked up as described earlier. The 10, 20, and 40% benzene–hexane eluates of an alumina chromatography were combined after ir examination, giving 2.32 g (36.1%) of **3**: ir ($CHCl_3$) ν 1660 cm^{-1} (vs); nmr ($CDCl_3$) τ 8.31 (d, 3 H, J = 1.25 Hz), 8.22 (d, 3 H, J = 1.0 Hz), 7.83 (s, 3 H), 6.35 (broad d, 2 H, J = 7.0 Hz), 4.97 (broad t, 1 H, J = 7.0 Hz), and 2.17 (multiplet, 4 H).

Registry No.—**3**, 957-78-8; **4**, 34638-45-4; **5**, 34638-46-5; **6**, 34638-47-6; **7**, 34638-48-7; **8**, 16511-15-2; **9**, 34638-50-1; **10**, 34638-51-2; **11**, 34638-52-3.

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A Convenient Synthesis of Benzocyclobutene

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In connection with current studies on strained heterocyclic systems, we required a supply of benzocyclobutene (**2**).[2] The preferred pathways to this compound

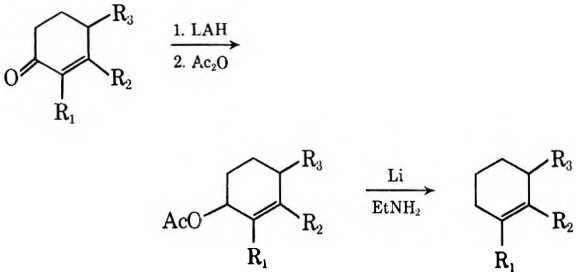
(1) Based on the Honors theses, Williams College, of S. J. Basta (1972) and P. M. Wege (1971).

(2) For a recent review of benzocyclobutene and its derivatives, see I. L. Klundt, *Chem. Rev.*, **70**, 471 (1970).

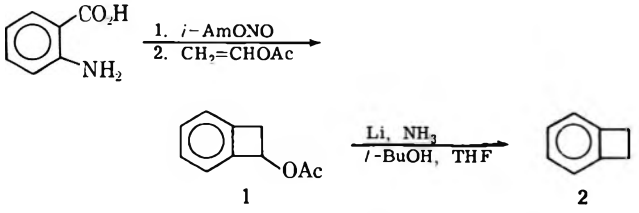
have previously involved high temperature pyrolyses *in vacuo* (without or with ultraviolet irradiation) of 1,3-dihydroisothianaphthene 2,2-dioxide[3,4] or hydrogenation of 1,2-diiodobenzocyclobutene.[5] The former method requires special apparatus, while the latter procedure involves lengthy purifications and a specially aged catalyst system.

Mindful of these limitations, we directed our attention to benzocyclobutenyl acetate (1), which is readily available from the cycloaddition of benzyne to vinyl acetate.[6] Although there are no reports in the literature of the reductive cleavage of **1** to **2**, the hydrogenolyses of benzylic and allylic esters are known. Two such procedures were studied in the present case. Treatment of **1** with tributyltin hydride failed to give any benzocyclobutene under the same free radical initiation conditions developed by Khoo and Lee[7] for a variety of benzylic esters; vpc analysis indicated that only starting material was recovered.

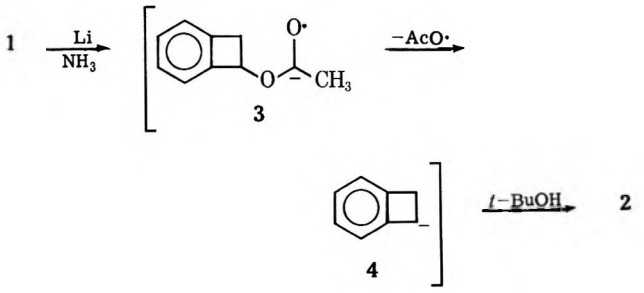
The conversion of **1** to **2** was smoothly effected, however, by a dissolving metal reduction analogous to the Henbest reaction. That process, which is a reductive cleavage of allylic acetates by lithium in ethylamine, is the key step in the reduction of α,β-unsaturated ketones



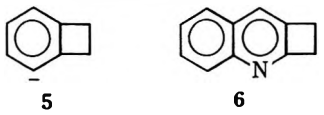
to the corresponding olefin.[8,9] In the present study some attention was directed toward the choice of solvent. Ethylamine was ineffectual and ethylenediamine[10] afforded five products, none of which was **2**; from the vpc analysis is was inferred that *o*-xylene and *o*-tolualdehyde were included in the product mixture. Liquid ammonia proved satisfactory as the solvent and moderately good yields of **2** were obtained. By this route benzocyclobutene is available in two steps by standard procedures.



In this reaction, which proceeds *via* the anion radical **3**, the intermediate anion **4** is produced by the loss of



the acetoxy radical. It is interesting that cleavage to the benzylic carbanion occurs as readily as it does, since this species is otherwise difficult to generate. Finnegan has reported that treatment of **2** with butylpotassium or amylsodium resulted in nuclear metalation ortho to the four-membered ring to give anion **5**.[11] It has also



been observed that hydrogen exchange at C-2 of 1,2-dihydrocyclobuta[*b*]quinoline (**6**) could not be effected by sodium ethoxide in ethanol-*O*-*d*.[12]

To our knowledge this reduction has not previously been applied to the cleavage of benzylic esters. Work is currently in progress to define the influence of the ester moiety and the range of benzylic groups.

Experimental Section

Boiling points are uncorrected. Instrumental data were obtained from a Perkin-Elmer 237-B infrared spectrophotometer; a Cary 14 ultraviolet spectrometer; a Varian T-60 nuclear magnetic resonance spectrometer, with tetramethylsilane as an internal standard; an AEI MS-9 mass spectrometer; and a Varian Aerograph 202B gas chromatograph, with a 12-ft 10% Dow 710 column.

Benzocyclobutene (2).—To a magnetically stirred solution of lithium (0.57 g, 0.082 g-atom) in liquid ammonia (45 ml) contained under a nitrogen atmosphere in a flask cooled by a Dry Ice–acetone bath was added dropwise a solution of benzocyclobutenyl acetate[6] (6 0 g, 0.037 mol) and *tert*-butyl alcohol (2.75 g, 0.037 mol) in anhydrous tetrahydrofuran (16 ml). The reaction solution was stirred for 2.5 hr at Dry Ice–acetone temperature, warmed to room temperature, quenched by the addition of solid ammonium chloride, diluted with water, allowed to remain overnight, and extracted with diethyl ether. The combined extract was washed (dilute HCl, water, and saturated NaCl solution), dried ($MgSO_4$), concentrated (vpc analysis of the residue indicated the presence of only **2**), and distilled to give 1.6 g (42%) of **2**: bp 70–71° (50 mm); $n^{21}D$ 1.5404; ir (film) 1462, 779, 715 cm^{-1}; nmr (CCl_4) δ 3.15 (s, 4); uv max (95% EtOH) 259.5 nm (ϵ 1230), 265.5 (1855), 271.5 (1830); mass spectrum (70 eV) *m/e* (rel intensity) 104 (100), 103 (47), 78 (38), 77 (19), 51 (20), 50 (10). The above spectral data were identical with those obtained with an authentic sample of **2** prepared by the hydrogenolysis of 1,2-diiodobenzocyclobutene.[5]

Registry No.—**2**, 4026-23-7.

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Cyclopentenones. An Efficient Synthesis of *cis*-Jasmone

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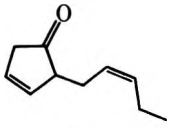
cis-Jasmone (**9**) is found in the flower oils of several varieties of Jasminum and is indispensable in the reproduction of jasmine fragrance from substances of synthetic origin. Total syntheses of *cis*-jasmone have been reported;[1] however, the routes employed are lengthy and suffer from low over-all yields. Jasmone has received considerable attention as a result of new methods of synthesizing 1,4 diketones which have been key intermediates leading to the cyclopentenone system.

We have developed a synthesis which allows the production of *cis*-jasmone in ~40% over-all yield from the readily available cyclopentadiene. In addition, cyclopentadiene is easily transformed into Δ^3-cyclopentenones with substitution adjacent to the carbonyl function (*e.g.*, **6**). Δ^3-Cyclopentenones of type **6** are potentially versatile intermediates and, moreover, they can be expected to equilibrate to the more stable α,β-unsaturated ketone (*e.g.*, **7**).



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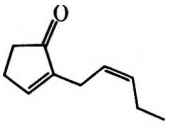

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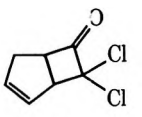
The starting point for the present synthetic scheme was the position-specific addition of dichloroketene to cyclopentadiene.[2] Treatment of a solution of cyclopentadiene and dichloroacetyl chloride in hexane at 0° with an excess of dry triethylamine in hexane resulted in an 85% yield of 7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one (**1**). Dechlorination was effected with excess zinc dust in glacial acetic acid at ~60° for approximately 1 hr to afford the bicyclic ketone **2** in >90% yield. Treatment of a solution of **2** in glacial acetic acid with 30% aqueous hydrogen peroxide at 0° for 24 hr produced in 90% yield the bicyclic lactone **3**.[3] The lactone **3** was reduced quantitatively to the hemiacetal **4** employing diisobutylaluminum hydride in toluene at −78°. The cis double bond present in jasmone was introduced in 70% yield by treatment of the hemiacetal **4** with the ylide derived from propyltriphenylphosphonium bromide in dimethyl sulfoxide.[4] The resulting alcohol could be oxidized with Jones reagent at 0° in acetone to afford a quantitative yield of the Δ^3-2-(*cis*-2-pentenyl)cyclopentenone (**6**).



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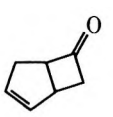

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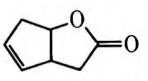

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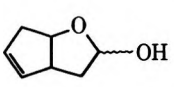

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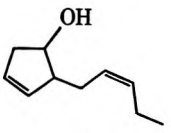

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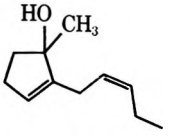
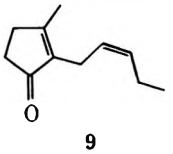


8

Initial attempts to isomerize the Δ^3-cyclopentenone **6** to the more stable α,β-unsaturated ketone **7** employing aqueous sodium hydroxide–ethanol proved disappointing. The predominant product was the desired dienone **7**; however, the yields ranged from 50 to 60%. Isomerization of the double bond was successfully accomplished in 90% yield with 2% aqueous sodium hydroxide at ~70°. The dienone **7** was transformed into *cis*-jasmone (**9**) by addition of methyllithium followed by oxidation of the resulting carbinol **8** with chromium trioxide.[1j] *cis*-Jasmone (**9**), $\nu_{max}^{CHCl_3}$ 1685 and 1640 cm^{-1}, was characterized by its 2,4-dinitrophenylhydrazone.[5] Ir and nmr spectra of synthetic *cis*-jasmone were identical with those of an authentic sample.[6]



9

The present synthesis allows the conversion of cyclopentadiene to *cis*-jasmone (**9**) in seven steps with an over-all yield of ~40%.

Experimental Section

Microanalyses were performed by the Spang Microanalytical Laboratories, Ann Arbor, Mich. Melting and boiling points are uncorrected. The following spectrometers were used: nuclear magnetic resonance (nmr), Varian T-60 and A-60D (in δ units, with TMS as internal reference in CCl_4 unless stated otherwise); infrared (ir), Perkin-Elmer Model 247 and Beckman IR-8; mass spectrometer (mass spectrum) LKB-9. Vapor phase chromatography (vpc) analyses were performed on a Varian Aerograph Model 90-P instrument using silicone rubber SE-30 and Carbowax 20 M columns. Pre-coated PLC silica gel F-254 Merck plates were used for preparative tlc.

7,7-Dichlorobicyclo[3.2.0]hept-2-en-6-one (**1**).—To a vigorously stirred solution of 27.2 g of freshly distilled cyclopentadiene, 30.5 g of dichloroacetyl chloride, and 200 ml of hexane (dried over molecular sieves) was added 21.7 g of dry triethylamine in 200 ml of hexane over a period of 1.5 hr. After stirring for 15 hr under an atmosphere of nitrogen, the reaction mixture was filtered and

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(6) Kindly supplied by International Flavors and Fragrances, Union Beach, N. J.

the filter cake was washed with hexane. The solvent was removed *in vacuo*, yielding a liquid weighing 35.2 g. Vacuum distillation afforded 30.0 g of product (~85%): bp 49–50° (0.3 mm); ir ($CHCl_3$) 1805 (C=O) and 1608 cm^{-1} (C=C); nmr (CCl_4) δ 2.70 (m, 2 H, $-CH_2-$), 4.10 (m, 2 H, bridgehead), 5.90 (m, 2 H, CH=CH).

Anal. Calcd for $C_7H_6Cl_2O$: C, 47.47; H, 3.42; Cl, 40.06. Found: C, 47.33; H, 3.48; Cl, 40.16.

Bicyclo[3.2.0]hept-2-en-6-one (2).—To a vigorously stirred suspension of 11.0 g (0.169 g-atom) of zinc dust in 15 ml of glacial acetic acid at room temperature was added dropwise 5.00 g (0.028 mol) of 7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one in 5 ml of glacial acetic acid. After addition was complete, the temperature was raised to and maintained at 70° for 40 min. Tlc analysis (pentane–I_2) after 40 min indicated no starting material remaining. The reaction mixture was cooled and treated with ether, and the zinc residue was filtered. The ethereal layer was washed with a saturated solution of Na_2CO_3 to remove the acetic acid and dried ($MgSO_4$). The solvent was removed on a rotary evaporator at *ca.* 10° and the product (2.89 g, 95%, homogeneous by tlc) was isolated by distillation: bp 60° (~15 mm); ir ($CHCl_3$) 1778 (C=O) and 1605 cm^{-1} (C=C); nmr (CCl_4) δ 2.4–2.9 (3 H, m), 3.0–3.6 (2 H, m), 3.6–4.0 (1 H, m), 5.80 (2 H, broad singlet).

Lactone of *cis*-2-Hydroxycyclopent-4-ene-1-acetic Acid (3).—To a solution of 3.24 g (30 mmol) of bicyclo[3.2.0]hept-2-en-6-one in 85 ml of 90% aqueous acetic acid cooled to 0° was added 8.15 g of 30% hydrogen peroxide in 70 ml of 90% aqueous acetic acid. The reaction was stirred at 0° for 24 hr (overnight). The product was extracted with ether and washed with 10% aqueous sodium sulfite and saturated sodium bicarbonate. The ether layer was dried over $MgSO_4$ and the solvent was removed *in vacuo*. Distillation afforded 3.35 g (90%) of lactone **3**: bp 70–71° (0.2 mm); ir ($CHCl_3$) 1760 (C=O) and 1605 cm^{-1} (C=C); nmr (CCl_4) δ 2.0–3.0 (4 H, m), 3.45 (1 H, m), 5.05 (1 H, m), 5.65 (2 H, m); mass spectrum *m/e* 124.

Anal. Calcd for $C_7H_8O_2$: C, 67.73; H, 6.49. Found: C, 67.83; H, 6.40.

Reduction of 3 to Hemiacetal 4.—Diisobutylaluminum hydride (6.39 g, 45 mmol) was added dropwise with stirring to a solution of pure lactone **3** (3.72 g, 30 mmol) in 200 ml of dry toluene cooled to −78°. The reaction mixture was stirred under nitrogen at −78° for 2 hr. The reaction was quenched by the addition of methanol (1.0 ml until gas evolution ceased) and was warmed to room temperature. After it was stirred for an additional 15 min, the reaction mixture was diluted with 100 ml of ether and 100 ml of 50% brine solution. The resulting emulsion was destroyed by the addition of 100 ml of an aqueous solution containing 5 ml of concentrated hydrochloric acid. An additional 150 ml of ether were added and the organic layer was separated. The aqueous layer was extracted with ether (2 × 50 ml). The combined organic extracts were dried over anhydrous sodium sulfate. Evaporation of the solvent *in vacuo* afforded 3.68 g (99%) of a clear liquid, bp 44–45° (0.01 mm), which was homogeneous by tlc (methylene chloride–methanol, 19:1, R_f 0.58): ir ($CHCl_3$) 3598, 3395 (OH), and 1605 cm^{-1} (C=C); nmr (CCl_4) δ 1.50–2.20 (2 H, m), 2.40–2.70 (2 H, m), 3.30 (1 H, m), 4.50–4.95 (2 H, m), 5.25–5.65 (3 H, m); mass spectrum *m/e* 108 (M − 18).

Anal. Calcd for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 66.75; H, 7.86.

2-(*cis*-2-Pentenyl)cyclopent-3-en-1-ol (5).—*n*-Propyltriphenylphosphonium bromide (17.71 g, 46 mmol), dried for 1 hr at 75° (0.2 mm), was dissolved in 90 ml of freshly distilled dimethyl sulfoxide (DMSO, distilled from CaH_2). To this solution at room temperature under nitrogen was added sodium methylsulfinylmethide, which yielded a red-orange solution. The anion of DMSO was prepared as follows: 2.90 g (69 mmol) of 57% sodium hydride dispersion was washed with dry pentane to remove the mineral oil. Dry DMSO (50 ml) was added and the mixture was stirred at 75° for *ca.* 1.5 hr.

Pure hemiacetal **4** (2.90 g, 23 mmol) in dry DMSO (10 ml) was added after 5 min. The reaction was stirred at room temperature for 2.5 hr, at which time tlc analysis (CH_2Cl_2–MeOH, 99:1) indicated no starting material remaining. The reaction was quenched by the addition of ice water and the mixture was extracted with hexane. The organic layer was washed with saturated sodium chloride solution, dried ($MgSO_4$), and evaporated to afford 3.35 g of crude product. Distillation of the product afforded 2.45 g (70%) of pure product, bp 48° (0.01 mm), homogeneous by tlc (CH_2Cl_2–MeOH, 99:1, R_f 0.60): ir ($CHCl_3$) 3600, 3460 (OH), and 1605 cm^{-1} (C=C); nmr (CCl_4) δ 1.00 (3 H, t), 1.80–2.80 (8 H, m), 4.30 (1H, m), 5.30–5.70 (4 H, m); mass spectrum *m/e* 152, 135 (M − 18).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.60. Found: C, 79.02; H, 10.64.

2-(*cis*-2-Pentenyl)-2-cyclopentenone (7).—A solution of 200 mg (1.32 mmol) of alcohol **5** in 10 ml of acetone was cooled to 0° and was treated dropwise with 1 equiv of standard Jones reagent (~0.4 ml). After 5 min, 0.2 ml of isopropyl alcohol was added and the mixture was extracted with pentane. The organic layer was subsequently washed with 10% $NaHCO_3$ and water, dried ($MgSO_4$), and evaporated *in vacuo* to afford 190 mg of crude Δ^3-cyclopentenone **6**, homogeneous by tlc (methylene chloride, R_f 0.75): ir ($CHCl_3$) 1749 cm^{-1} (C=O); nmr (CCl_4) δ 0.98 (3 H, t), 1.70–2.60 (5 H, m), 2.60–3.00 (2 H, m), 5.35 (2 H, m), 6.05 (2 H, broad singlet).

The crude ketone **6** was treated with 8.0 ml of aqueous 2% NaOH solution under nitrogen at ~70°. Isomerization to the more stable α,β-unsaturated ketone **7** was essentially complete after *ca.* 1 hr. The mixture was cooled, extracted with pentane, washed with water, dried (Na_2SO_4), and evaporated, affording 166 mg of dienone **7**, bp 67–68° (0.05 mm), which was homogeneous by tlc (methylene chloride, R_f 0.53): ir ($CHCl_3$) 1690 (C=O) and 1630 cm^{-1} (C=C); nmr (CCl_4) δ 0.98 (3 H, t), 1.80–3.00 (8 H, m), 5.40 (2 H, m), 7.18 (1 H, broad singlet).

***cis*-Jasmone (9).**—To a solution of 140 mg (0.93 mmol) of ketone **7** in 3 ml of anhydrous ether cooled to 0° was added 1.2 ml (2.0 mmol) of 1.66 *M* methyllithium in ether. After 15 min at room temperature the mixture was quenched with cold water. The product was extracted with pentane, washed with water, dried (Na_2SO_4), and evaporated *in vacuo* to afford 149 mg of alcohol **8**, ir ($CHCl_3$) 3610, 3430 cm^{-1}.

The crude carbinol was dissolved in 3 ml of ether, cooled to 0°, and treated dropwise with a solution of 100 mg of CrO_3 in 1.0 ml of aqueous 5% H_2SO_4. Stirring was continued for an additional 15 min at 0°. The reaction was quenched by the addition of water and the mixture was extracted with pentane. The organic layer was washed with 10% $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated to give 138 mg (84% yield) of crude *cis*-jasmone (**9**). A pure sample was obtained by preparative tlc on silica gel plates using methylene chloride–methanol (99:1): ir ($CHCl_3$) 1685 (C=O) and 1640 cm^{-1} (C=C); nmr (CCl_4) δ 1.00 (3 H, t), 2.0 (3 H, s), 2.1–2.6 (6 H, m), 2.85 (2 H, d), 5.25 (2 H, m). Ir and nmr spectra and retention time on vpc were identical with those of an authentic[6] sample of *cis*-jasmone.

Registry No.—**1**, 5307-99-3; **2**, 13173-09-6; **3**, 34638-25-0; **4**, 34638-26-1; **5**, 34638-27-2; **6**, 34638-28-3; **7**, 34638-28-3; **9**, 4907-07-7.

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Ketenimines. II.[1] Lone-Pair Effects on Nuclear Magnetic Resonance Properties of the Cumulenic π System

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Allene (**1**) can be considered the parent molecule for a number of heterocumulene analogs of which the nitro-

(1) See G. Krow, *Angew. Chem.*, **83**, 455 (1971); *Angew. Chem., Int. Ed. Engl.*, **7**, 435 (1971), for a review of ketenimine chemistry.

gen compounds carbodiimides **2** and ketenimines **3**[1] are representative examples. Evidence obtained from spectral measurements is in agreement with a dissymmetric ground state configuration having orthogonal π systems for each of these cumulenes **1–3**.[2] The

$H_2C{=}C{=}CH_2$ (**1**) $\quad RN{=}C{=}NR$ (**2**) $\quad R_2C{=}C{=}NR$ (**3**)

structural similarities of **1–3**, however, tend to overshadow the inherent difference in the electronic properties of the heterocumulenes **2** and **3** resulting from the presence on nitrogen of invertible unshared electron pairs. We here wish to report the importance of interaction of the nitrogen lone pair electrons with cumulene π electrons on determining shifts in the nmr spectra of ketenimines.

From comparison of chemical shift data for comparably substituted allenes (Table I) and ketenimines (Table II), a greater shielding effect as measured by $\Delta\delta$ (Table II) for the allenic hydrogen in ketenimines is indicated. The difference $\Delta\delta$ reflects variations in diamagnetic shielding of the allenic hydrogen, and in the associated electric fields and diamagnetic anisotropies of the cumulenic systems.

Table I

Chemical Shift Values (δ) for Allenic Hydrogen as a Function of Geminal Substituent X in Allenes (R = R′ = Alkyl)

$XCH{=}C{=}CRR'$ (**4**)

Compd	Substituent X	Chemical shift, δ[a]
4a	H	4.4–5.0[b–d]
4b	Alkyl	4.8–5.1[e–f]
4c	$CHMeCH_2OH$	5.1[g]
4d	COMe	5.7[h]
4e	Cl	5.8[i]
4f	Ph	5.9[c]

[a] Spectra were reported neat or in dilute CCl_4. It was reported that there were no marked solvent effects on shifts[d,i] [b] D. Koster and A. J. Danti, *J. Phys. Chem.*, **69**, 486 (1965). [c] R. Fantazier and M. Poutsma, *J. Amer. Chem. Soc.*, **90**, 5490 (1968). [d] R. Ferguson, *J. Phys. Chem.*, **68**, 1594 (1964). [e] R. Kullnig and F. Nachod, *ibid.*, **67**, 1361 (1963). [f] S. Landor, A. Patel, P. Whiter, and P. Greaves, *J. Chem. Soc. C*, 1223 (1966). [g] R. Macomber, *J. Org. Chem.*, **36**, 999 (1971). [h] M. Martin, G. Martin, and R. Couffignal, *J. Chem. Phys.*, **49**, 1985 (1968). [i] G. Reddy, L. Mandell, and J. Goldstein, *J. Amer. Chem. Soc.*, **83**, 4729 (1961).

Table II

Chemical Shift Values (δ) for Allenic Hydrogen as a Function of Geminal Substituent X in Ketenimines (R = Alkyl)

$XCH{=}C{=}NR$ (**5**)

Compd	Substituent X	Chemical shift, δ ($CDCl_3$)	$\Delta\delta$, ppm[a]
5a	CH_2CMe_2Cl	3.5	1.62[b,c]
5b	Isopropyl[d]	4.06	0.75–1.05
5c	COMe	4.4[e]	1.3[f]
5d	Ph	4.8[g]	1.1
5e	Cl	5.05	0.75[c]

[a] $\Delta\delta$ = δ(allene) − δ(ketenimine). Shifts are to higher field for ketenimines. [b] Compared to allene X = $CHMeCH_2OH$. [c] R. Lloyd, Ph.D. Thesis, Clemson University, 1968. [d] *N*-phenyl. [e] CCl_4. [f] R. Woodward and D. Woodman, *J. Amer. Chem. Soc.*, **89**, 3169 (1966). [g] The chemical shift of the allenic hydrogen varied less than 0.1 ppm between determinations of neat liquid and dilute solutions of $CDCl_3$ and CCl_4. Since marked solvent shifts were not observed for allenes, $\Delta\delta$ does not measure bulk diamagnetic susceptibility.

(2) For the carbodiimide structure, see (a) G. Rapi and G. Sbrana, *J. Amer. Chem. Soc.*, **93**, 5213 (1971). (b) F. A. L. Anet, J. C. Jochims, and C. H. Bradley, *ibid.*, **92**, 2557 (1970). (c) For the ketenimine structure, see J. Jochims and F. Anet, *ibid.*, **92**, 5524 (1970).

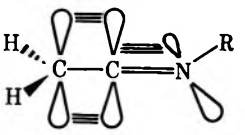

Figure 1.—A p-orbital representation of interaction of the lone pair orbital and the adjacent π-bond.

In order to estimate the diamagnetic shielding effect of the ketenimine nitrogen on the shift of the allenic hydrogen, the hydridization at the terminal allenic carbons for allene and ketenimine were determined from the ^{13}C–H coupling constants, which are insensitive to medium and anisotropy effects.[3] A coupling value of 170 Hz for **3d** indicates similar hybridization as found in allene, $^2J_{^{13}C-H}$ = 168 Hz. Hybridization differences can thus account for less than 0.1 ppm of shift.[3,4] The coupling ^3J = 5.73 Hz for **3b**, of similar magnitude to that in allenes,[5] is evidence for similar electron distribution for allenes and ketenimines at the terminal allenic carbon, and negligible deshielding electron withdrawal from this carbon by the electronegative nitrogen.

In addition to the similarity of electron distribution at the allenic carbon indicating little contribution from resonance form **6**, which would result in a shielding

$R_2C{=}C{=}NR \longleftrightarrow R_2\bar{C}{-}C{\equiv}\overset{+}{N}R$ (**3** ↔ **6**)

contribution, Anet[2c] has found a barrier to configurational inversion of aryl–alkyl ketenimines of 9–12 kcal/mol, consistent with a dissymmetric ground state **3**. By addition of Eu(fod)$_3$[6] to *N*-isopropylphenylmethylketenimine we have confirmed the availability of the ketenimine nitrogen lone pair. The electron pair is, however, somewhat less available than that of a nitrile. The above data thus indicate little influence of nitrogen by diamagnetic shielding on shift of the allenic proton. On the basis of the Eu(fod)$_3$ coordination with nitrogen, the electrostatic effect would result in a downfield shift of the allenic proton resonance since the dipole moment vector has its negative end (shielding) toward the electron withdrawing nitrogen and its positive end (deshielding) toward the allenic hydrogen.[8]

$+ \longrightarrow -$

$R_2C{=}C{=}NR$

The enhanced shielding, which is sufficient to over-

(3) D. Rosenberg and W. Drenth, *Tetrahedron*, **27**, 3893 (1971).

(4) J. W. Emsley, J. Feeney, and L. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. II, Pergamon Press, London, 1967, pp 1014, 1016, 1021. The effect of the α-phenyl on ^{13}C–H coupling is minimal. Typical couplings are Ph–CH_3 = 126 Hz, Ph_2CH_2 = 127 Hz. The allenic nitrogen might have been expected to cause a small change in hydridization; coupling ^{13}C–H for CH_3CN = 136 Hz; $CH_3C{\equiv}CH$ = 132 Hz.

(5) See Table II, ref *b*, *c*, *e*, *g*; ^3J = 4.75–6.65 Hz in allenes.

(6) Addition of Eu(fod)$_3$ to *N*-isopropylmethylphenylketenimine resulted in extrapolated shifts at Eu(fod)$_3$/substrate ratio = 1 of NC*H* = 6, $CHCH_3$ = 3, CH_3C = 1.0 ppm. ΔEu values determined using Eu(dpm)$_3$ were one-sixth as large. The ketenimine electron pair is a weaker coordinator than a nitrile, ΔEu for $N{\equiv}CCH$ = 3–7 cps.[7]

(7) J. K. M. Sanders and D. H. Williams, *J. Amer. Chem. Soc.*, **93**, 641 (1971).

(8) J. W. ApSimon and H. Beierbeck, *Can. J. Chem.*, **49**, 1328 (1971), have found electrostatic and magnetic anisotropy effects equally important in a theoretical treatment of shielding effects for the carbonyl group.

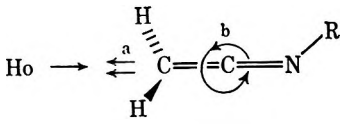

Figure 2.—Shielding of allenic hydrogens in ketenimines: Ho = applied field; a = induced magnetic lines of force shielding the allenic hydrogen; b = circulating π electrons.

come any diamagnetic or electric field deshielding contributions, can be attributed to an effect of electron donation from the rear lobe of the nitrogen sp^2-hybridized lone-pair orbital to the coplanar π system of the allenic double bond (Figure 1). The charge increase at the central allenic carbon will reinforce the magnetic field of the ring current[3] by an increase in the rotating charge of the cumulene and will result in enhanced diamagnetic anisotropic shielding of the allenic hydrogen (Figure 2).

The present results indicate that, while analogy between the geometries of cumulenes and heterocumulenes is valid, heteroatom effects on electronic properties are not to be neglected. It can also be predicted that heteroatoms will effect rotational barriers and bond lengths and energies in cumulenes.[9]

(9) Although the double bond stretching frequencies for C=N (1690–1640 cm^{-1}) and C=C (1680–1620 cm^{-1})[10] are similar, the stretching frequencies for C=C=C (1970–1950 cm^{-1}),[10] N=C=C (2050–2000 cm^{-1}),[1] and N=C=N (2155–2130 cm^{-1})[10] indicate a bond tightening effect of the heteroatom which might be attributed to lone pair–π electron overlap.

Experimental Section

Nmr spectra were recorded on a Varian XL-100-15, in 10% solutions with $DCCl_3$ or CCl_4 as solvents and tetramethylsilane as external standard.

Materials. ***N*-Phenylisopropylketenimine (3b)** was synthesized from *N*-phenylisovaleric acid amide[11] in 39% yield according to the general procedure of Stevens and French.[12] The yellow oil, bp 52–53° (0.15 mm), was characterized by its ketenimine absorption, 2025 cm^{-1} (neat): nmr ($CDCl_3$) δ 7.26, 4.06 (d, ^3J = 5.73 Hz), 4.49 (m), 1.10 (d, J = 7 Hz).

***N*-Isopropylphenylketenimine (3d)** was similarly prepared from *N*-isopropylphenylacetamide in 54% yield. The yellow oil, bp 53–54° (0.15 mm), was identified by a 2010-cm^{-1} (neat) absorption: nmr ($CDCl_3$) δ 7.88, 4.76 (d, ^5J = 1.96 Hz), 3.81 (m), 1.30 (d, J = 7 Hz). Coupling ^{13}C–H of the allenic hydrogen of 170 Hz was determined from the ^{13}C side bands of the proton spectrum and was an average of four determinations. The allenic hydrogen had nmr δ 4.64 neat and at increasing dilutions with CCl_4.

Anal. Calcd for $C_{11}H_{15}NO$: C, 74.56; H, 8.53; N, 7.90. Found: C, 74.28; H, 8.46; N, 7.78.

Ketenimines **3b** and **3d** could be reconverted to the corresponding amides by hydrolysis.

Registry No.—**3b**, 34621-16-4; **3d**, 34621-17-5.

(10) C. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, pp 34, 61, 263.

(11) W. Autenrieth and G. Thomae, *Chem. Ber.*, **57**, 423 (1924).

(12) C. L. Stevens and J. C. French, *J. Amer. Chem. Soc.*, **76**, 4398 (1954).

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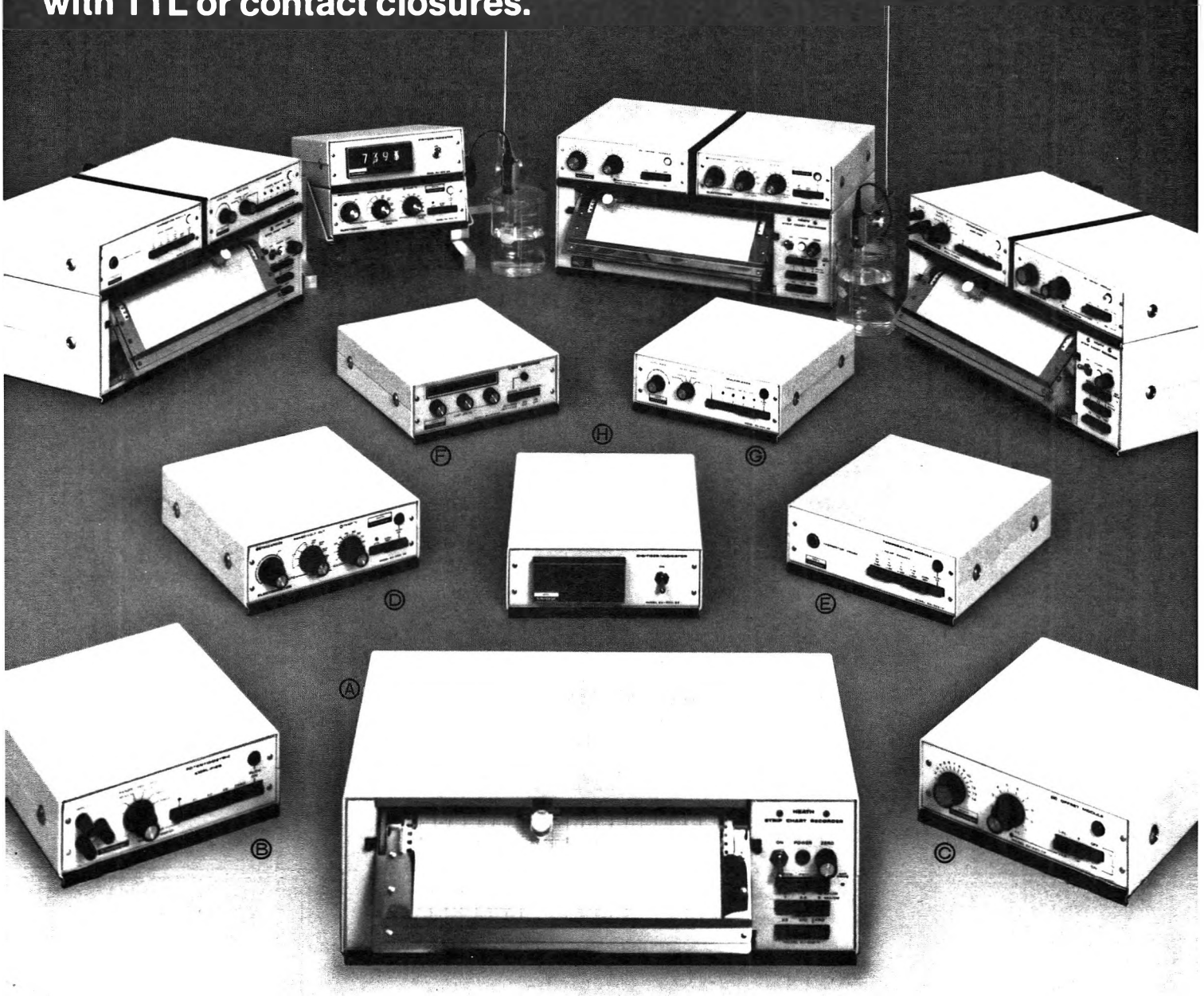

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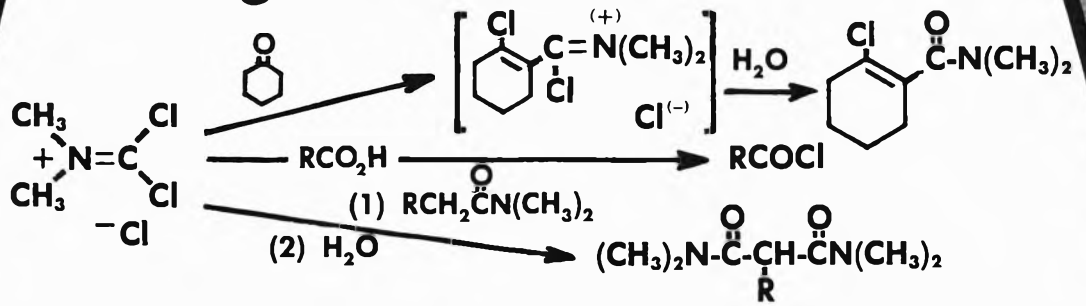

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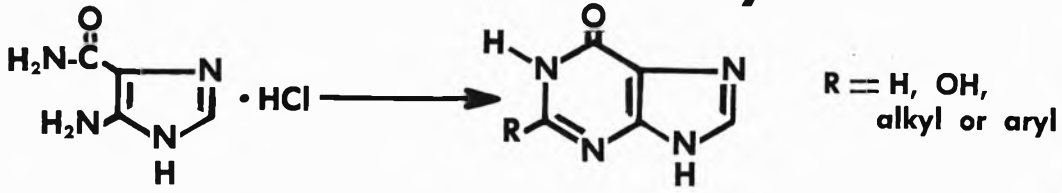

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