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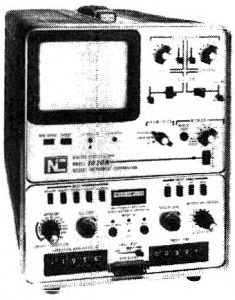

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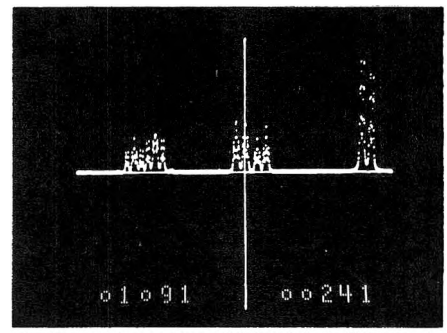

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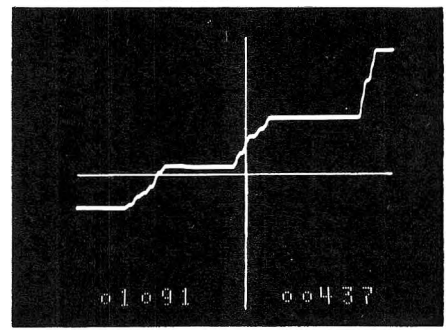

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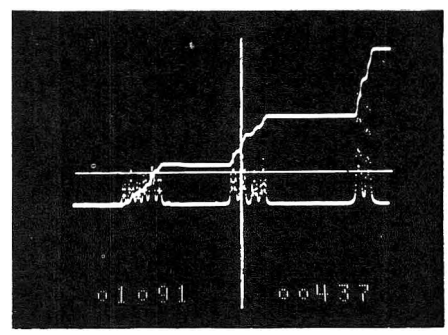

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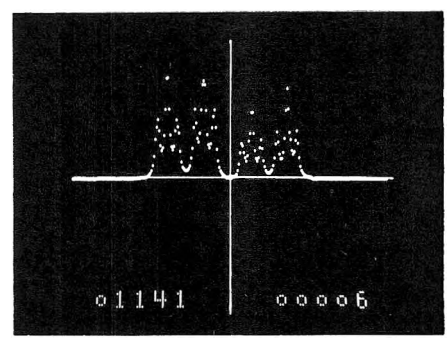

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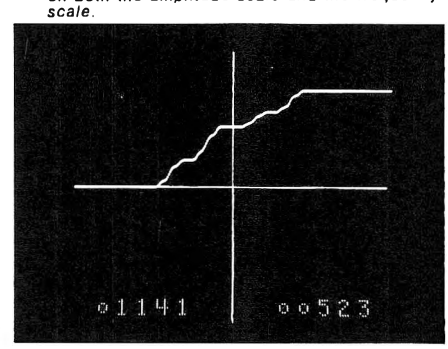

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The Nature and Composition of Taft–Hancock Steric Constants

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Department of Agricultural Chemistry, Kyoto University, Kyoto, Japan

Received November 7, 1972

The Taft steric, E_s, and the Hancock corrected steric, E_s^c, constants of a set of various alkyl- and heteroatom-substituted groups were analyzed as to whether they are separable into components. The analyses were carried out by means of the equation $E_s(CR_1R_2R_3) = aE_s(R_1) + bE_s(R_2) + cE_s(R_3) + d$, where $E_s = E_s$ or E_s^c and $E_s(R_1) \geqq E_s(R_2) \geqq E_s(R_3)$. For the set of 37 groups, the correlation was surprisingly good for E_s^c values, 98% of variance of the data being elucidated. The finding that the linear combination of three α substituents is capable of describing the steric constant of the parent group indicates that the relative importance of the steric repulsion effect and steric hindrance of motions in any one of the E_s^c values is unchanged so that an isokinetic relationship holds between relative enthalpies and entropies of activation for the steric course of ester reactions.

In order to estimate the steric effect in aliphatic reactions quantitatively, the Taft E_s constants defined by eq 1 are most widely used.[1] The expression (k_R/

$$E_s = \log(k_R/k_{Me})_A \quad (1)$$

$k_{Me})_A$ refers to the ratio of the rate constant of acid-catalyzed hydrolysis of esters of the type RCOOEt to that of MeCOOEt.

Since the E_s value is determined by the relative activation free energy from the unsaturated initial state to the saturated transition state of the ester hydrolysis, Hancock and his coworkers considered that a hyperconjugation effect of α hydrogen may contribute to the estmate of E_s values.[2] They defined an E_s^c (corrected steric) constant as shown in eq 2, separating

$$E_s^c = E_s - 0.306(3 - n_H) \quad (2)$$

the hyperconjugation effect from the "true steric effect." In eq 2, n_H is the number of α hydrogen atoms.

In the course of structure–reactivity studies on various sets of aliphatic amines with various lone-pair electron acceptors, we have found that the steric and polar effects of three N substituents of amines can be separated in the form of eq 3, where k is either a rate

$$\log k = \rho^*\Sigma\sigma^* + aE_s^c1 + bE_s^c2 + cE_s^c3 + d \quad (3)$$

or an equilibrium constant, ρ^*, a, b, c, and d are constants, and $\Sigma\sigma^*$ is the summation of the Taft σ^* values of three N substituents. E_s^c1, E_s^c2, and E_s^c3 relate to the N substituents R_1, R_2, and R_3, denoted according to the sequence of their magnitude, *i.e.*, $E_s^c1 \geqq E_s^c2 \geqq E_s^c3$. The use of E_s instead of E_s^c values was found to yield poorer results.[3]

The total steric effect of three N substituents, R_1, R_2, and R_3, on a certain electron acceptor is similar in nature, if not identical, to that of three α substituents R_1, R_2, and R_3 on the reaction center in the transition state of ester hydrolysis as suggested by Taft (Figure 1).[4] We have assumed that the E_s^c value of a certain group, $CR_1R_2R_3$, may be expressed by a linear combination of those of three α substituents, R_1, R_2, and R_3, as shown in eq 4, where $E_s^c1 \geqq E_s^c2 \geqq E_s^c3$ and

$$E_s^c(CR_1R_2R_3) = aE_s^c1 + bE_s^c2 + cE_s^c3 + d \quad (4)$$

a, b, c, and d are constants which are determined by means of the method of least squares.

The purpose of the work in this paper is to obtain supporting evidence on the above assumption by analyzing the mutual relationship among E_s^c values expressed in terms of eq 4 and to contribute to a better understanding of the nature and composition of steric constants. Since the particular use of E_s^c values has been viewed with skepticism by some workers,[5] we have compared the quality of correlation between eq 4 and its counterpart for E_s values.

Analyses.—First, we have analyzed E_s and E_s^c values directly with those of three α substituents for 26 primary, secondary, and tertiary alkyl groups from the Taft's original tabulation.[1] Equations 5 and 6 are derived for E_s and E_s^c values, respectively. In these and the following equations, n is the number of data points used for the correlation, s is the standard deviation, and r is the correlation coefficient. The figures in

(1) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 597.

(2) K. Hancock, E. A. Meyers, and B. J. Yager, *J. Amer. Chem. Soc.*, **83**, 4211 (1961).

(3) T. Fujita, C. Takayama, and M. Nakajima, to be published.

(4) Reference 1, p 673.

(5) K. Bowden, N. B. Chapman, and J. Shorter, *J. Chem. Soc.*, 5239 (1963).

$$E_s(CR_1R_2R_3) = \underset{(\pm 0.655)}{-2.467} + \underset{(\pm 0.554)}{0.924\,E_s1} + \underset{(\pm 0.319)}{0.774E_s2} + \underset{(\pm 0.334)}{0.438E_s3} \quad (5)$$

$n = 26$, $s = 0.613$, $r = 0.898$, $F_{3,25} = 30.4$

$$E_s^c(CR_1R_2R_3) = \underset{(\pm 0.586)}{-2.347} + \underset{(\pm 1.598)}{4.589E_s^c1} + \underset{(\pm 0.425)}{0.958E_s^c2} + \underset{(\pm 0.318)}{0.630E_s^c3} \quad (6)$$

$n = 26$, $s = 0.647$, $r = 0.917$, $F = 38.9$

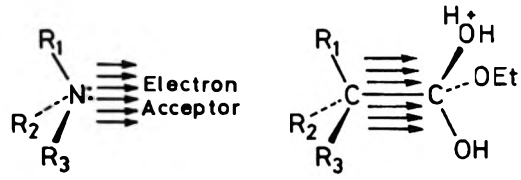

Figure 1.—Resemblance of total steric effect of three substituents.

parentheses are the 95% confidence intervals. Both eq 5 and 6 are significant at better than the 99.5% confidence level ($F_{3,26,0.005} = 5.41$). The quality of correlation is slightly better for E_s^c values than for E_s values in terms of the F value. Although the correlations are far from complete, the E_s and E_s^c values can be separated into their components much better than we might anticipate. With increasing substitutions at the α carbon, the steric effect is increased "telescopically" in such series as Me, Et, *i*-Pr, and *t*-Bu. However, the telescoping effect is not general and is not observed with successive α-methyl substitutions on neo-Pent and neopentylmethyl groups. Thus, we might expect that the composition of steric constants is too complex to be expressed by a simple relationship such as eq 5 or 6. Almost 80% of variance in the steric constant data is elucidated by eq 5 and 6.

In elaborating the correlations, we have considered that E_s or E_s^c values of some α substituents could not always represent their steric effects properly. The E_s and E_s^c values of primary alkyl groups are generally well predicted by eq 5 and 6 except for those of *i*-Pent and neopentylmethyl groups where the calculated values are considerably lower than their original values. For these two groups, the steric constants of the component R_3 may not represent the true situation. The *i*-Bu and neo-Pent groups at the α carbon could rotate around the C_α–C_β axis so that the effect of *i*-Pr and *t*-Bu groups at the β carbon might be minimized. We assume that the steric effect of *i*-Bu and neo-Pent substituents at the α carbon can be simulated by that of the *n*-Pr group.

If the components at the α carbon are congested in secondary and tertiary groups, their orientation would be limited and "effective" steric constants might differ from their original values. For these groups, the total number of hydrogens at β carbon atoms could be taken as a measure of congestion. The maximum number is six for secondary groups at *i*-Pr and nine for tertiary group at *t*-Bu. The less the number of β hydrogens, *i.e.*, the more substituted the β carbon atoms by other alkyl groups, the more congested would be the α substituents. We have assumed that, when the number of β hydrogens becomes less than four for secondary and less than six for tertiary alkyl groups, the steric effect of α comoonents, in particular, that of groups of CH_2R' type, is represented by a different E_s or E_s^c value.

If the steric effects of both the groups R_2 and R_3 of CH_2R' type are originally moderate, one of these groups would be forced to direct its R′ moiety forward so as to exaggerate its steric effect. Thus, in diethylcarbinyl, di-*n*-propylcarbinyl, and triethylcarbinyl groups, the effective steric effect of one of the component Et and *n*-Pr groups could be expressed by the E_s or E_s^c value of the *i*-Pr group. If the steric effect of the group R_3 is large enough, the group R_2 of the CH_2R' type would be oriented in such a way as to minimize the effect of R′ on the group R_3 and the reaction center. For *i*-Bu and neo-Pent groups as the component R_2 in diisobutylcarbinyl, dineopentylcarbinyl, and methylneopentyl-*tert*-butylcarbinyl groups, the steric effect could be similar to that of the *n*-Pr group.

For methyl-*tert*-butylcarbinyl and dimethyl-*tert*-butylcarbinyl groups both the groups R_2 and R_3 are of the symmetrical top type. It is difficult to choose other substituents the E_s or E_s^c values of which are capable of describing the effective steric effects of groups R_2 and R_3. Probably, the effect of the *t*-Bu group would be much greater than that anticipated by its usual E_s and E_s^c values. These two groups are not submitted to further correlations. In Table I, the above assumptions are summarized.

TABLE I
CONFORMATIONALLY LIMITED GROUPS

	Original groups[a]			No. of	Groups which exhibit "effective" steric effect[b]		
	R_1	R_2	R_3	β H	R_1	R_2	R_3
Primary	H	H	*i-Bu*	2	H	H	*Pr*
	H	H	*neo-Pent*	2	H	H	*Pr*
Secondary	H	Et	*Et*	4	H	Et	*i-Pr*
	H	Pr	*Pr*	4	H	Pr	*i-Pr*
	H	*i-Bu*	i-Bu	4	H	*Pr*	i-Bu
	H	*neo-Pent*	neo-Pent	4	H	*Pr*	neo-Pent
	H	Me	*t-Bu*	3	H	Me	(*t*-Bu)
Tertiary	Et	Et	*Et*	6	Et	Et	*i-Pr*
	Me	Me	*t-Bu*	6	Me	Me	(*t*-Bu)
	Me	*neo-Pent*	*t*-Bu	5	Me	*Pr*	*t*-Bu

[a] The component group the conformation of which is significantly limited is italicized. [b] The group the steric constant of which is taken to simulate the "effective" steric effect is italicized. *t*-Bu group is shown with parentheses; see text.

With the use of effective E_s or E_s^c values for conformationally limited α substituents in Table I, the correlations are repeated. The results are shown in Table II and eq 7 and 8. The correlation for E_s values is still not acceptable. By eq 7, E_s values of secondary and tertiary groups are only very poorly predicted. On the other hand, the correlation for E_s^c values is much improved. Equation 8 is able to interprete 98% of the variance in E_s^c data. Thus, the assumptions made above for conformations of α substituents appear to be justified and the E_s^c value seems to be better than E_s for the scale of steric effects. Encouraged by this result, we have attempted to extend the analyses to other groups the α substituents of which include heteroatoms. To this end, the steric constants of heteroatoms should be evaluated.

Recently, Charton has analyzed quantitatively the dependence of E_s values on group dimensions expressed in terms of van der Waals radii.[6] For example, the

(6) M. Charton, *J. Amer. Chem. Soc.*, **91**, 615 (1969).

TABLE II
STERIC CONSTANTS OF ALKYL GROUPS

Groups	Component α substituents[a] R1	R2	R3	Component E_s values E_s1	E_s2	E_s3	E_s values Orig[d]	Calcd[e]	Component E_s^c values E_s^c1	E_s^c2	E_s^c3	E_s^c values Orig	Calcd[f]
Me	H	H	H	1.24	1.24	1.24	0.00	0.53	0.32	0.32	0.32	0.00	−0.17
Et	H	H	Me	1.24	1.24	0.00	−0.07	−0.27	0.32	0.32	0.00	−0.38	−0.37
Pr	H	H	Et	1.24	1.24	−0.07	−0.36	−0.32	0.32	0.32	−0.38	−0.67	−0.62
Bu	H	H	Pr	1.24	1.24	−0.36	−0.39	−0.51	0.32	0.32	−0.67	−0.70	−0.81
Pent	H	H	Bu	1.24	1.24	−0.39	−0.40	−0.52	0.32	0.32	−0.70	−0.71	−0.83
i-Pent	H	H	*i*-Bu*	1.24	1.24	−0.36	−0.35	−0.51	0.32	0.32	−0.67	−0.66	−0.81
n-Oct	H	H	*n*-Hept	1.24	1.24	−0.33[b]	−0.33	−0.49	0.32	0.32	−0.64[b]	−0.64	−0.79
	H	H	neo-Pent*	1.24	1.24	−0.36	−0.34	−0.51	0.32	0.32	−0.67	−0.65	−0.81
i-Bu	H	H	*i*-Pr	1.24	1.24	−0.47	−0.93	−0.58	0.32	0.32	−1.08	−1.24	−1.07
neo-Pent	H	H	*t*-Bu	1.24	1.24	−1.54	−1.74	−1.27	0.32	0.32	−2.46	−2.05	−1.97
	H	H	Bz[c]	1.24	1.24	−0.38	−0.38	−0.52	0.32	0.32	−0.69	−0.69	−0.82
	H	H	$BzCH_2$	1.24	1.24	−0.38	−0.45	−0.52	0.32	0.32	−0.69	−0.76	−0.82
	H	H	c-Hex	1.24	1.24	−0.79	−0.98	−0.78	0.32	0.32	−1.40	−1.29	−1.28
i-Pr	H	Me	Me	1.24	0.00	0.00	−0.47	−1.30	0.32	0.00	0.00	−1.08	−1.01
sec-Pent	H	Et	Et*	1.24	−0.07	−0.47	−1.98	−1.67	0.32	−0.38	−1.08	−2.59	−2.46
sec-Hept	H	Pr	Pr*	1.24	−0.36	−0.47	−2.11	−1.91	0.32	−0.67	−1.08	−2.72	−3.03
	H	*i*-Bu*	*i*-Bu	1.24	−0.36	−0.93	−2.47	−2.21	0.32	−0.67	−1.24	−3.08	−3.14
	H	neo-Pent*	neo-Pent	1.24	−0.36	−1.74	−3.18	−2.73	0.32	−0.67	−2.05	−3.79	−3.66
sec-Bu	H	Me	Et	1.24	0.00	−0.07	−1.13	−1.35	0.32	0.00	−0.38	−1.74	−1.25
	H	Me	neo-Pent	1.24	0.00	−1.74	−1.85	−2.43	0.32	0.00	−2.05	−2.46	−2.34
t-Bu	Me	Me	Me	0.00	0.00	0.00	−1.54	−2.28	0.00	0.00	0.00	−2.46	−2.10
	Et	Et	Et*	−0.07	−0.07	−0.47	−3.80	−2.70	−0.38	−0.38	−1.08	−4.72	−4.86
	Me	Me	neo-Pent	0.00	0.00	−1.74	−2.57	−3.41	0.00	0.00	−2.05	−3.49	−3.43
	Me	neo-Pent*	*t*-Bu	0.00	−0.36	−1.54	−4.00	−3.58	0.00	−0.67	−2.46	−4.92	−5.03

[a] Conformationally limited groups are indicated with asterisk. Their steric constants are taken as shown in Table I. [b] Steric constants of *n*-Hept are taken as those of *n*-Oct. [c] Bz = benzyl. [d] Original values from ref 1. [e] Calculated by eq 7. [f] Calculated by eq 8.

$$E_s(CR_1R_2R_3) = \underset{(\pm 0.596)}{-2.282} + \underset{(\pm 0.510)}{0.789E_s1} + \underset{(\pm 0.363)}{0.832E_s2} + \underset{(\pm 0.340)}{0.648E_s3} \qquad n = 24,\ s = 0.499,\ r = 0.921 \qquad (7)$$

$$E_s^c(CR_1R_2R_3) = \underset{(\pm 0.195)}{-2.104} + \underset{(\pm 0.516)}{3.429E_s^c1} + \underset{(\pm 0.252)}{1.978E_s^c2} + \underset{(\pm 0.118)}{0.649E_s^c3} \qquad n = 24,\ s = 0.191,\ r = 0.992 \qquad (8)$$

E_s values of CH_2X, CHX_2, and CX_3 groups including the group of X = H are linearly dependent on van der Waals radius, $r_v(X)$, of the heteroatom, X, such as halogens and O and S in OCH_3 and SCH_3 groups. Equations 9–11 indicate the situation where a, a', a'',

$$E_s(CH_2X) = ar_v(X) + c \qquad (9)$$

$$E_s(CHX_2) = a'r_v(X) + c' \qquad (10)$$

$$E_s(CX_3) = a''r_v(X) + c'' \qquad (11)$$

c, c', and c'' are constants. He also pointed out that, for symmetrical top-type groups such as CX_3 and CH_3, either a maximum or a minimum value of the group van der Waals radius, $r_v(CX_3, max)$ or $r_v(CX_3, min)$, calculated by means of trigonometry can be used to correlate with their E_s value. With the use of an average of Charton's r_v(max) and r_v(min) values, Kutter and Hansch have derived eq 12 for symmetrical top-

$$E_s = \underset{(\pm 0.55)}{3.484} - \underset{(\pm 0.22)}{1.839}\, r_v(CX_3, ave) \qquad n = 6,\ s = 0.132,\ r = 0.996 \qquad (12)$$

type groups including H.[7] Substituting the $r_v(X)$ values of halogens, O, and S into eq 12, they have estimated E_s values of symmetric monoatomic substituents as well as of OCH_3 and SCH_3, as shown in Table III.

Adopting these E_s values for α-heteroatom substituents, eq 13 is derived for 37 groups including 24 alkyl- and 13 heteroatom-substituted groups. Although E_s values of the heteroatom-substituted groups are well predicted in general, the situation for some of the secondary and tertiary alkyl groups is not improved much above eq 7, as shown in Table IV.

TABLE III
E_s AND E_s^c VALUES OF HALOGENS OCH_3, OPh, AND SCH_3

Functions	$r_v(X)$	E_s[b]	E_s^c[c]
F	1.47	0.78	−0.02
Cl	1.75	0.27	−0.18
Br	1.85	0.08	−0.23
I	1.98	−0.16	−0.31
OCH_3[a]	1.52	0.69	−0.05
OC_6H_5[a]	1.52	0.69	−0.05
SCH_3[a]	1.80	0.17	−0.21

[a] Calculated using oxygen or sulfur radius only. [b] Calculated by eq 12. [c] Calculated by eq 17.

For evaluating E_s^c values of heteroatom substituents, the procedure using the relationship between E_s^c and r_v(ave) for symmetrical top-type groups including H cannot be applied. While both E_s and E_s^c values of CH_3 are equal to each other, being zero, the E_s^c values of H and CX_3 (X = halogen and CH_3) are taken to be $0.306\ (3 - n_H) = 0.92$ unit lower than the corresponding E_s values. Thus, the correlation of E_s^c with r_v(ave) is obviously poorer than that in eq 12. If the E_s^c is really free from the hyperconjugation effect and a measure of the "true" steric effect, the apparent lack of linear correlation with the van der Waals radius might

(7) E. Kutter and C. Hansch, *J. Med. Chem.*, **12**, 647 (1969).

$$E_s(CR_1R_2R_3) = -2.532 + 0.739E_s1 + 0.926E_s2 + 0.440E_s3 \quad (13)$$
$$(\pm 0.382)\ (\pm 0.371)\ (\pm 0.276)\ (\pm 0.215)$$

n	s	r
37	0.429	0.925

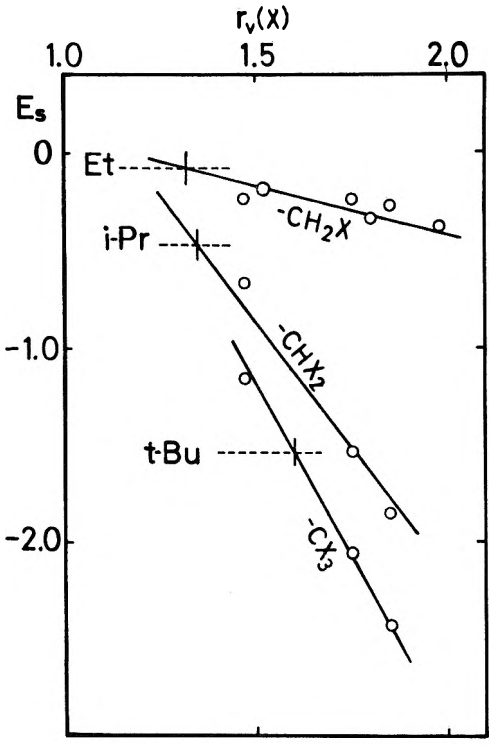

Figure 2.—Plot of E_s *vs.* r_v (X).

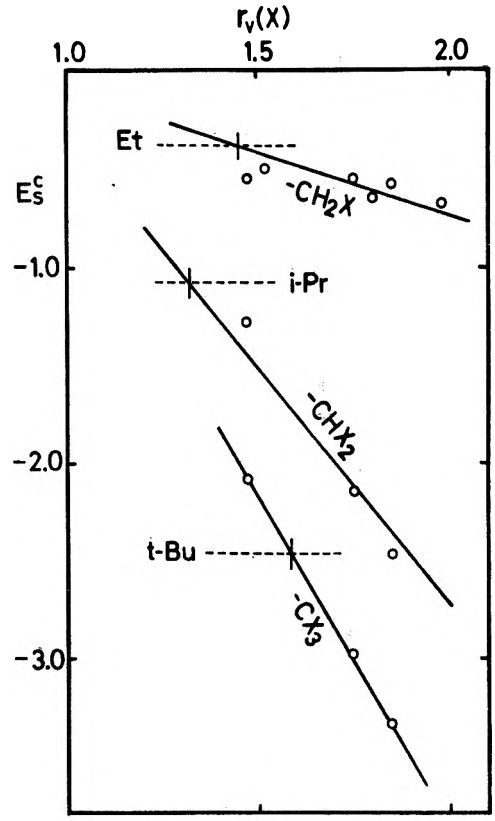

Figure 3.—Plot of E_s^c *vs.* r_v (X).

be due to the fact that the r_v(ave) values such as those used for eq 12 do not represent the "effective" steric dimensions for some groups.

There are some conflicts in the estimate of r_v(ave) or r_v(X) of the CH_3 group (X = CH_3), even for the relation with E_s values. The E_s value of $C(CH_3)_3$ is 0.89 unit larger than that of CBr_3, indicating that the effective steric size of CH_3 is considerably smaller than that of Br. Yet, from eq 12, the E_s value of Br is estimated as being quite close to that of CH_3, since r_v(X) of Br and r_v(ave) of CH_3 are taken as 1.85 and 1.97 Å, respectively. Moreover, the linear relationships between $E_s(CH_2X$, CHX_2, CX_3) and r_v(X) as shown in eq 9–11 do not hold for the groups of X = CH_3. The E_s values of Et, *i*-Pr, and *t*-Bu groups are too large to be elucidated by r_v(ave) and even by r_v(min) of the Me group. The effective size of Me should be considerably smaller than that represented by r_v(min), 1.76 Å.

Figures 2 and 3 indicate the situation, showing that the effective value of $r_v(CH_3)$ might be estimated as 1.3–1.5 Å. The three lines in these figures which correlate E_s or E_s^c values with r_v(X) should intersect the abscissa at the same point when X = H; *i.e.*, CH_2X = CHX_2 = CX_3 = CH_3. The most probable r_v(X) values for X = CH_3 and X = H are estimated by means of the relation expressed as eq 14. In this equation, *a*, *b*, *c*, and

$$r_v(X) = aE_s(CH_2X) + bE_s(CHX_2) + cE_s(CX_3) + d \quad (14)$$

d are constants and each of the E_s terms is applied only to each type of group; *i.e.*, for CH_2X type groups, $a \gtrless 0$ and $b = c = 0$. For 12 groups in Table V where X = halogen, OCH_3, and SCH_3, eq 15 and 16 are derived. The correlation coefficients of these equations are not very high. However, the standard deviations are rather small and the *F* tests show that the correlations are significant at better than 99% level of probability ($F_{3,8,0.01} = 7.59$).

From eq 15, r_v(H) is 1.16 Å on the basis of E_s values, which agrees with its usually adopted value, 1.20 Å. However, eq 16 with E_s^c values show that the effective radius of H is around 0.87 Å. By substituting the E_s value of Et, *i*-Pr, and *t*-Bu groups into the first, second, and third term of eq 15, respectively, the values 1.31, 1.34, and 1.60 Å are obtained for r_v(Me). The average of these three is 1.41 Å, which could be regarded as the most probable effective radius of Me. Similarly, from eq 16, the values 1.43, 1.31, and 1.55 Å are derived. The average, 1.43 Å, can be taken as r_v(Me) on the basis of E_s^c values. The effective value of r_v(Me), 1.41–1.43 Å, seems rather low compared with the usually adopted value, 2.00 Å, or r_v(ave), 1.97 Å. Charton has recognized that r_v(min), 1.72 Å, is always a better scale for elucidating the steric effect of Me than r_v(max) or r_v(ave).[6] The dimensions of the hydrogen atom are so small that the net effect of Me could be represented by the one even lower than the r_v(min) value. Since the effective value of r_v(Me) is close to the van der Waals radius of a naked carbon atom, 1.60 Å,[8] the group Me could be regarded as having the character of a single atom type substituent. Thus, the correlation between E_s and r_v(ave) shown as eq 12 seems to require reexamination, at least for ester reactions. For inter-

(8) "Handbook of Biochemistry," H. A. Sober, Ed., Chemical Rubber Co., Cleveland, Ohio, 1970, p J-3.

TABLE IV

STERIC CONSTANTS OF ALKYL- AND HETEROATOM-SUBSTITUTED GROUPS

	Component α-substituents[a]			Component E_s values			E_s values		Component E_s^c values			E_s^c values	
Groups	R_1	R_2	R_3	E_s1	E_s2	E_s3	Orig[d]	Calcd[e]	E_s^c1	E_s^c2	E_s^c3	Orig	Calcd[f]
Me	H	H	H	1.24	1.24	1.24	0.00	0.15	0.32	0.32	0.32	0.00	−0.29
Et	H	H	Me	1.24	1.24	0.00	−0.07	−0.40	0.32	0.32	0.00	−0.38	−0.47
Pr	H	H	Et	1.24	1.24	−0.07	−0.36	−0.43	0.32	0.32	−0.38	−0.67	−0.69
Bu	H	H	Pr	1.24	1.24	−0.36	−0.39	−0.56	0.32	0.32	−0.67	−0.70	−0.85
Pent	H	H	Bu	1.24	1.24	−0.39	−0.40	−0.57	0.32	0.32	−0.70	−0.71	−0.87
i-Pent	H	H	*i*-Bu*	1.24	1.24	−0.36	−0.35	−0.56	0.32	0.32	−0.67	−0.66	−0.85
n-Oct	H	H	*n*-Hept	1.24	1.24	−0.33[b]	−0.33	−0.55	0.32	0.32	−0.64[b]	−0.64	−0.84
	H	H	neo-Pent*	1.24	1.24	−0.36	−0.34	−0.56	0.32	0.32	−0.67	−0.65	−0.85
i-Bu	H	H	*i*-Pr	1.24	1.24	−0.47	−0.93	−0.61	0.32	0.32	−1.08	−1.24	−1.09
neo-Pent	H	H	*t*-Bu	1.24	1.24	−1.54	−1.74	−1.08	0.32	0.32	−2.46	−2.05	−1.88
	H	H	Bz[c]	1.24	1.24	−0.38	−0.38	−0.57	0.32	0.32	−0.69	−0.69	−0.87
	H	H	$BzCH_2$[c]	1.24	1.24	−0.38	−0.45	−0.57	0.32	0.32	−0.69	−0.76	−0.87
	H	H	c-Hex	1.24	1.24	−0.79	−0.98	−0.75	0.32	0.32	−1.40	−1.29	−1.27
i-Pr	H	Me	Me	1.24	0.00	0.00	−0.47	−1.55	0.32	0.00	0.00	−1.08	−1.16
sec-Pent	H	Et	Et*	1.24	−0.07	−0.47	−1.98	−1.82	0.32	−0.38	−1.08	−2.59	−2.60
sec-Hept	H	Pr	Pr*	1.24	−0.36	−0.47	−2.11	−2.09	0.32	−0.67	−1.08	−2.72	−3.23
	H	*i*-Bu*	*i*-Bu	1.24	−0.36	−0.93	−2.47	−2.29	0.32	−0.67	−1.24	−3.08	−3.32
	H	neo-Pent*	neo-Pent	1.24	−0.36	−1.74	−3.18	−2.65	0.32	−0.67	−2.05	−3.79	−3.78
sec-Bu	H	Me	Et	1.24	0.00	−0.07	−1.13	−1.58	0.32	0.00	−0.38	−1.74	−1.38
	H	Me	neo-Pent	1.24	0.00	−1.74	−1.85	−2.31	0.32	0.00	−2.05	−2.46	−2.33
t-Bu	Me	Me	Me	0.00	0.00	0.00	−1.54	−2.53	0.00	0.00	0.00	−2.46	−2.12
	Et	Et	Et*	−0.07	−0.07	−0.47	−3.80	−2.86	−0.38	−0.38	−1.08	−4.72	−4.69
	Me	Me	neo-Pent	0.00	0.00	−1.74	−2.57	−3.30	0.00	0.00	−2.05	−3.49	−3.29
	Me	neo-Pent*	*t*-Bu	0.00	−0.36	−1.54	−4.00	−3.54	0.00	−0.67	−2.46	−4.92	−4.97
CH_2OMe	H	H	OMe	1.24	1.24	0.69	−0.19	−0.10	0.32	0.32	−0.05	−0.50	−0.50
CH_2Cl	H	H	Cl	1.24	1.24	0.27	−0.24	−0.28	0.32	0.32	−0.18	−0.55	−0.58
CH_2F	H	H	F	1.24	1.24	0.78	−0.24	−0.06	0.32	0.32	−0.02	−0.55	−0.48
CH_2Br	H	H	Br	1.24	1.24	0.08	−0.27	−0.37	0.32	0.32	−0.23	−0.58	−0.60
CH_2SMe	H	H	SMe	1.24	1.24	0.17	−0.34	−0.33	0.32	0.32	−0.21	−0.65	−0.59
CH_2I	H	H	I	1.24	1.24	−0.16	−0.37	−0.47	0.32	0.32	−0.31	−0.68	−0.65
CH_2OPh	H	H	OPh	1.24	1.24	0.69	−0.33	−0.10	0.32	0.32	−0.05	−0.64	−0.50
CHF_2	H	F	F	1.24	0.78	0.78	−0.67	−0.48	0.32	−0.02	−0.02	−1.28	−1.22
$CHCl_2$	H	Cl	Cl	1.24	0.27	0.27	−1.54	−1.18	0.32	−0.18	−0.18	−2.15	−1.66
$CHBr_2$	H	Br	Br	1.24	0.08	0.08	−1.86	−1.44	0.32	−0.23	−0.23	−2.47	−1.79
CF_3	F	F	F	0.78	0.78	0.78	−1.16	−0.85	−0.02	−0.02	−0.02	−2.08	−2.23
CCl_3	Cl	Cl	Cl	0.27	0.27	0.27	−2.06	−1.95	−0.18	−0.18	−0.18	−2.98	−3.15
CBr_3	Br	Br	Br	0.08	0.08	0.08	−2.43	−2.36	−0.23	−0.23	−0.23	−3.35	−3.43

[a] Conformationally limited groups are shown with asterisk. For their steric constants, see Table I. [b] Taken as those of *n*-Oct. [c] Bz = benzyl. [d] From ref 1. [e] Calculated by eq 13. [f] Calculated by eq 19.

TABLE V

$r_v(X)$ *vs.* E_s AND E_s^c VALUES, DATA FOR EQUATIONS 15 AND 16

				$r_v(X)$					$r_v(X)$	
Groups	$E_s(CH_2X)$	$E_s(CHX_2)$	$E_s(CX_3)$	Orig	Calcd[a]	$E_s^c(CH_2X)$	$E_s^c(CHX_2)$	$E_s^c(CX_3)$	Orig	Calcd[b]
CH_2F	−0.24			1.47	1.66	−0.55			1.47	1.68
CH_2Cl	−0.24			1.75	1.66	−0.55			1.75	1.68
CH_2Br	−0.27			1.85	1.72	−0.58			1.85	1.73
CH_2I	−0.37			1.98	1.93	−0.68			1.98	1.88
CH_2OMe	−0.19			1.52	1.56	−0.50			1.52	1.61
CH_2SMe	−0.34			1.80	1.87	−0.65			1.80	1.83
CHF_2		−0.67		1.47	1.42		−1.28		1.47	1.39
$CHCl_2$		−1.54		1.75	1.75		−2.15		1.75	1.75
$CHBr_2$		−1.86		1.85	1.87		−2.47		1.85	1.89
CF_3			−1.16	1.47	1.49			−2.08	1.47	1.48
CCl_3			−2.06	1.75	1.74			−2.98	1.75	1.74
CBr_3			−2.43	1.85	1.85			−3.35	1.85	1.85

[a] Calculated by eq 15. [b] Calculated by eq 16.

$$r_v(X) = 1.164 - 2.065E_s(CH_2X) - 0.379E_s(CHX_2) - 0.281E_s(CX_3) \quad (15)$$
$$(\pm 0.235)\ (\pm 0.873)\qquad (\pm 0.176)\qquad (\pm 0.132)$$

$n = 12$, $s = 0.095$, $r = 0.892$, $F_{3,8} = 10.3$

$$r_v(X) = 0.865 - 1.485E_s^c(CH_2X) - 0.413E_s^c(CHX_2) - 0.295E_s^c(CX_3) \quad (16)$$
$$(\pm 0.414)\ (\pm 0.721)\qquad (\pm 0.210)\qquad (\pm 0.151)$$

$n = 12$, $s = 0.107$, $r = 0.861$, $F_{3,8} = 7.60$

molecular interactions such as enzyme-inhibitor and drug-receptor complex formations where the thickness of substituents on an aromatic ring plays a critical role, the E_s values, being linearly related to the thickness of substituents, have been found to be useful parameters.[7]

The effective value, 0.87 Å, for hydrogen on the basis of E_s^c values is also considerably lower than its usually adopted value, 1.20 Å. As shown in Figure 4, for CX_3 type substituents, the variation in their dimension is largest toward a direction which takes 70.5° (= 180° − 109.5°) with the central axis. In this case, the $r_v(CX_3, ave)$ values take care of the variation in the covalent bond radii of X. On the other hand, for single-atom substituents, the variation in their dimension is largest along the central axis, being determined by their covalent and van der Waals radii. In this case, the increase in the van der Waals radius which is necessarily accompanied with the elongation of the C–X bond would not be reflected on the increase in the steric effect so remarkably as that for CX_3 type substituents. The situation can be illustrated in Figure 5, where the plot of E_s^c values *vs.* effective or average r_v values for H-, CH_3-, and CX_3-type substituents, regarding CH_3 as having characters of CX_3 type and also single atom type substituent, results in biphasic lines. In Figure 5, the line connecting points for H and CH_3 is regarded as representing the relation of E_s^c with effective r_v value of single-atom substituents. The slope is −0.57, as shown in eq 17. This value is about $^1/_3$ of that of the regression line expressed as eq 18 for CX_3-type substituents. The ratio is acceptable since it is close to the cosine of 70.5°, the angle between two directions along which the variations in dimensions of X and CX_3 substituents are most sensitive. On this basis, the effective value of an H-substituent radius, 0.87 Å, would not be considered as an unreasonable estimate.

$$E_s^c(X) = 0.821 - 0.571r_v(X) \quad (17)$$

$$E_s^c(CX_3) = \underset{(\pm 0.756)}{2.610} - \underset{(\pm 0.285)}{1.860}r_v(ave) \quad \begin{matrix} n & s & r \\ 5 & 0.126 & 0.997 \end{matrix} \quad (18)$$

The E_s^c values of single-atom substituents, including OCH_3 and SCH_3, which are shown in Table III are estimated by means of eq 17. With these values for α-heteroatom substituents, the E_s^c values of 37 groups shown in Table IV are analyzed to give eq 19. The quality of correlation is slightly poorer than that of eq 8 but still good enough to be acceptable. The values of the slope of each E_s^c term and intercept are practically identical with those of eq 8. Although the E_s^c values of $CHCl_2$ and $CHBr_2$ are poorly predicted (*vide infra*), it would be reasonable to conclude that, on the whole, the steric constants are separable into components even for the heteroatom substituents.

$$E_s^c(CR_1R_2R_3) = \underset{(\pm 0.151)}{-2.118} + \underset{(\pm 0.468)}{2.982}E_s^c1 + \underset{(\pm 0.273)}{2.160}E_s^c2 + \underset{(\pm 0.116)}{0.570}E_s^c3 \quad \begin{matrix} n & s & r \\ 37 & 0.232 & 0.985 \end{matrix} \quad (19)$$

Discussion

The above analyses strongly support the hypothesis that the steric constant of aliphatic groups is composed of three components. Although the relative merits of two sets of constants, E_s and E_s^c, should be compared with the use of reactivity and equilibrium data involving steric effects, E_s^c values, in particular those of alkyl groups, are suggested to be superior to E_s values as the scale of steric effect. The failure in predicting those of secondary and tertiary alkyl groups is the most serious drawback in E_s values.

We have adopted in this work E_s^c values which are estimated assuming that the hyperconjugation effect is −0.306 log unit per α hydrogen.[2] Whether or not the hyperconjugation effect of α hydrogen is unchanged regardless of substituents being alkyl- or heteroatom-substituted groups is still open to further discussions. However, the good correlations obtained for eq 8 and 19 would indicate that the value −0.306 is reasonable at least as a first approximation. The concept of CF hyperconjugation, which was suggested at one time, has been proved to be fallacious recently.[9]

For the acid hydrolysis of esters, the step of attack of a water molecule on the protonated ester at the sp^2 carbon atom is rate limiting. The stable conformations of esters and also of protonated esters have been generally considered to be the eclipsed forms.[10,11] The most stable form is shown in Figure 6, where the bulkiest α substituent, R_3, is eclipsed with the carbonyl or $^+$C–OH except for dihalo acetates.[11] The water molecule would attack the sp^2 carbon from the side sterically least hindered. In this situation, the steric effect of the R_1 group would play a dominant role. At the same time as the attack of water molecule, the coordination number of the sp^2 carbon is increased from three to four and the resultant sp^3 structure would take a staggered form, as shown in Figure 7. The larger the size of the component R_2, the less favorable would be the process, since nonbonded repulsion with R_2 becomes greater in the sp^3 structure than before. When the size of the R_3 group increases, two opposed effects would emerge. One is that the attack of a water molecule is less favored and the other is that the release of the $^+$C–OH group from the eclipsed form to the less hindered staggered conformation would be facilitated. These two effects would be more or less compensated by each other. Thus, the activation process would be most sensitive to the steric effect of R_1 and least to that of R_3. The coefficient of E_s^c terms in eq 8 and 19 can be understood on this basis. Although each of the component E_s^c values can be further separable into three subcomponents, it should represent the "total" steric effect for each of the α substituents in the right side of these equations.

The most poorly predicted E_s^c values in eq 19 are those of dihalomethyl (CHX_2) groups. For dihaloacetic acid esters, Brown has proposed that they exhibit a two-fold barrier to internal rotation and the form I is more stable than the form II in Figure 8.[11] Thus, the situation where a water molecule attacks the sp^2 carbon is different from that shown in Figure 7. If the protonated esters also maintain the same conformations as shown in Figure 8, the groups R_1, R_2, and R_3 would

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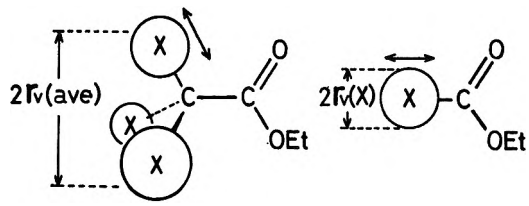


Figure 4.—The direction along which the variation in group dimensions is most sensitive to structural variation (⟷).

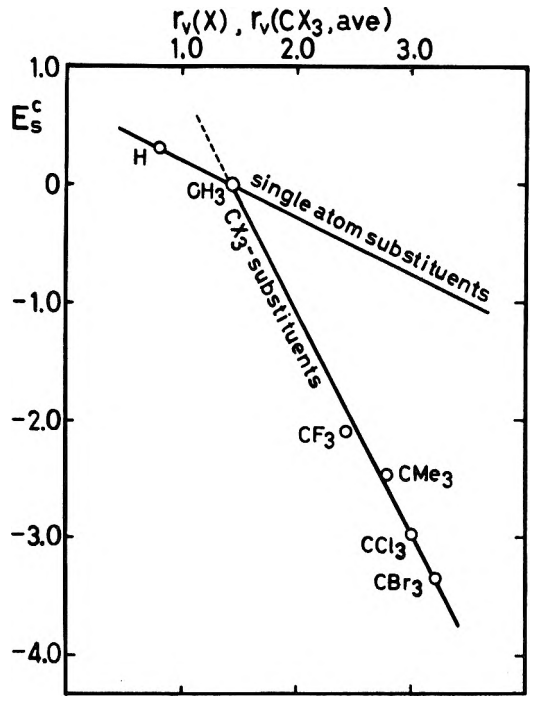


Figure 5.—Plot of E_s^c *vs.* effective $r_v(X)$ or $r_v(CX_3, ave)$ value of symmetric top-type groups.

correspond to X, X, and H, respectively, in either of these two conformations, so that the component E_s^c values should be taken as $E_s^c1 = E_s^c2 = E_s^c(X)$ and $E_s^c3 = E_s^c(H)$, the sequence of magnitude being $E_s^c1 = E_s^c2 < E_s^c3$. The calculated values by means of eq 19 with the use of these component values are, in effect, smaller than the values earlier predicted, but even smaller than the actual values. Thus, it could be anticipated that the dihalo acetates are attacked by the water molecule partly in these conformations.

In Taft's orginal tabulation of steric constants, 50 groups are included.[1] Out of these, the cycloalkyl groups and groups where at least one of the α components is phenyl are excluded from the analyses, since steric constants of cyclic polymethylene and phenyl groups are not available. We are now able to calculate E_s^c values of tri-, tetra-, penta-, and hexamethylene cyclic groups by substituting E_s^c values of H and cyclobutyl, -pentyl, -hexyl, and -heptyl groups into eq 8, and combining the E_s^c2 and E_s^c3 terms. As shown in Table VI, the steric effects of polymethylene groups are

TABLE VI

E_s^c VALUES OF POLYMETHYLENE CYCLIC GROUPS

Groups	$E_s^c/2$
$(CH_3)_4<$	0.13
$(CH_2)_4<$	−0.04
$(CH_2)_5<$	−0.15
$(CH_2)_6<$	−0.27

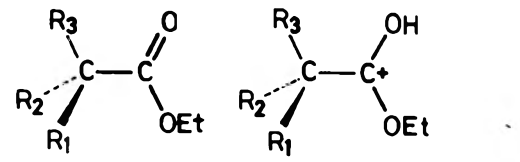


Figure 6.—The most stable form of esters and their protonated intermediates.

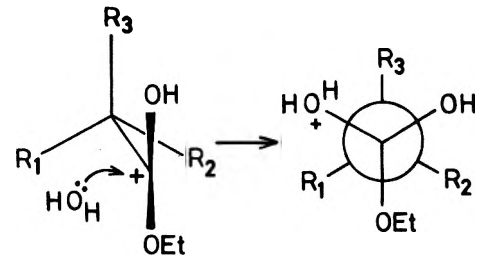
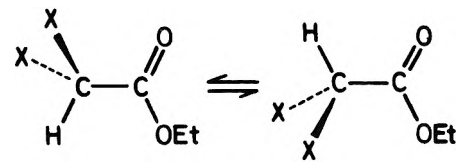


Figure 7.—The rate-determining step of ester hydrolysis.



I II

Figure 8.—Rotamers of dihalo acetates.

generally low. At the most, the E_s^c value of one of two bidentate hexamethylene ligands, −0.27, is still higher than that of Et, −0.38. In cyclohexyl and cycloheptyl groups, the reaction center is located at the equatorial position with regard to the ring system, so that the effect of the tied-up polymethylene chain would be minimized. The steric constant for the phenyl group as the α components could be compared with that of Et, as shown in Table VII. The E_s^c value of the di-

TABLE VII

COMPARISON OF STERIC EFFECTS IN Ph AND Et GROUPS

Component α substituents			E_s^c value	Components of equivalent steric effect			E_s^c value calcd[a]
H	H	Ph	−0.69	H	H	Et	−0.62
H	Me	Ph	−1.80	H	Me	Et	−1.25
H	Et	Ph	−2.11	H	Et	Et	−2.01
H	Ph	Ph	−2.37	H	Et	*i*-Pr	−2.59

[a] Calculated by eq 8.

phenylmethyl group can be explained by the congestion of two α-phenyl groups.

The steric constants of $ClCH_2CH_2$– and $CH_3OCH_2CH_2$– groups are also not included in the analyses, since they are only very poorly predicted on preliminary calculations. For these groups, the steric effect is much higher than expected. Probably, β-Cl and $-OCH_3$ groups would be directed toward the reaction center as shown in Figure 9. The positive charge at the reaction center would attract the lone-pair-carrying substituents at the β-carbon atom.

It is interesting to test the applicability of eq 8 by examining the steric constants of alkyl-*o*-biphenylylcarbinyl groups determined by Bowden and his associates recently.[5] Their E_s values, listed in Table VIII,

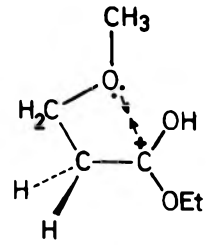
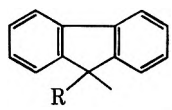


Figure 9.—Interaction of β substituents with the reaction center.

TABLE VIII
STERIC CONSTANTS OF
ALKYL-*o*-BIPHENYLYLCARBINYL GROUPS



No.	R	E_s[a]	E_s^c Orig	E_s^c Calcd[b]
1	H	−1.10	−1.71	−1.55
2	Me	−1.73	−2.65	−2.65[c]
3	Et	−1.97	−2.89	−3.49
4	*i*-Pr	−3.30	−4.22	−3.94
5	*t*-Bu	−4.12	−5.04	−4.83

[a] Taken from ref 5. [b] Calculated by eq 8. [c] Taken as the standard.

are obtained from the rate constants of acid-catalyzed esterification of acids. From the E_s^c value of group 2 in Table VIII, we can calculate that of one of two ligands of *o*-biphenylyl as being −0.21 by using eq 8. With this value, the E_s^c values of homologous groups are calculated. Except for group 3, the predictions by means of eq 8 are fairly good. The steric effect of the conformationally fixed phenyl group can be considered quite low, being between those of methyl and ethyl.

According to Taft, the steric effect in ester reactions is, in fact, a combination of two effects, *i.e.*, steric strain effect and steric hindrance of motions.[12] The activation energy due to repulsive interactions of component α substituents with the reaction center would be increased by an increase in the steric strain effect of substituents. The entropy of activation would be decreased by a loss of internal motions in the transition state relative to the initial state. It has been generally considered that "no substituent leads to increased steric strain without an accompanying increased steric hindrance of motions, *i.e.*, that the parallel retarding effects are usually observed in relative enthalpies and entropies of activation, $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$, resulting from structural variation."[12] The two parallel effects are not necessarily linearly related with each other.

The present work indicates that, although a simple additive principle does not hold for the steric constant of any substituent, the constants expressed in terms of E_s^c can be expressed by a linear combination of those of three α components. Thus, the relative importance of two effects, steric strain and steric hindrance of motions, in any one of E_s^c values should be kept constant, at least for ester reactions. The variation in the steric repulsion effect and steric hindrance of motions according to the structural variation, which are formulated by $\Delta\Delta H^{\ddagger}$ and $-T\Delta\Delta S^{\ddagger}$, are related proportionally so that an isokinetic relationship would hold between two parallel effects.

The above discussions present possible rationale for the linear relationship among steric constants of aliphatic groups. The critical assumptions used for the analyses, such as conformational restrictions for some α substituents and biphasic relations between E_s^c and r_v for symmetrical top-type groups, would be plausible enough as far as the present discussions are concerned. However, it is emphasized that, in the absence of theoretical knowledges, the present result should be taken as an empirical relationship among steric effect constants for ester reactions. In fact, we have found that the total steric effect of three N substituents on various types of electron acceptors is similarly expressed by a linear combination of E_s^c constants but the values of slope associated with each E_s^c term are different from those of eq 8 or 19, and substituents for which conformational restrictions should be considered are not identical with those in Table I.[3] Here, a relationship such as eq 8 or 19 cannot be extended directly to estimate the total steric effect of N substituents. It might be also possible that further studies on steric mechanisms for other reactions reveal deviations from the simple linear combinations. As Miller has pointed out, multiple variations which give rise to linear relationships such as eq 8 or 19 are special cases of more generally expected ones which contain cross terms.[13] Thus, it is urgently desirable for further work to establish the realm of validity of this type of quantitative approach to the steric course of reaction mechanisms.

(12) Reference 1, p 665.

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Application of the Hammett Equation to Nonaromatic Unsaturated Systems. IX. Electrophilic Addition to Olefins. X. Nucleophilic Addition to Olefins

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Data for fifteen sets of rates of electrophilic addition to substituted ethylenes were correlated with the extended Hammett equation. Significant correlations were obtained for the majority of the sets studied. The results show that, while in the majority of the sets the localized effect is predominant, in a minority of the sets the delocalized effect is predominant. The results are accounted for in terms of the reaction mechanism. Sets for which the localized effect is predominant are believed to react *via* a bridged intermediate, whereas sets for which the delocalized effect predominates are thought to react *via* a carbonium ion intermediate. Data on the orientation observed in the addition of BH_3 to substituted ethylenes were also studied. The orientation is governed largely by the delocalized effect. Data for eight sets of rates of nucleophilic addition to substituted ethylenes were correlated with the extended Hammett equation using σ_R constants, with the extended equation using σ_R^- constants, and with the equation $Q_X = \beta\sigma_{R,X} + h$. Best results were obtained with the equation above. Of the eight sets examined, six gave significant correlation. The large values of β observed are in accord with rate-determining formation of a carbanion intermediate. The transition state is closer to the carbanion than it is to the reactants. Although values of β obtained from correlation with the equation are temperature dependent, they are not a linear function of $1/T$.

In a previous paper of this series,[1] the effect of substituents on diene and dienophile reactivity in the Diels–Alder reaction was studied. It seemed of interest to extend our investigation to the effect of substituents upon electrophilic addition to the double bond. The first attempt to correlate rates of electrophilic addition to the double bond with a linear free-energy relationship was reported by de la Mare[2] who used the σ_p^+ constants and the simple Hammett equation to correlate rates of addition of chlorine to 3,3-disubstituted acrylic acids. The Taft modification of the Hammett equation has been used by Dubois and coworkers to correlate the rates of bromination of substituted ethylenes.[3-6] The use of eq 1, in which the E_S

$$Q_X = \rho^*\Sigma\sigma^*_X + \delta\Sigma^*E_{S,X} + h \quad (1)$$

values are the Taft steric parameter, has been reported by Dubois and Bienvenue-Goetz.[6] A correlation of values of $\Delta\Delta G^{\ddagger}_{\psi}$ with σ_R° constants was reported by Dubois and coworkers[7] for bromination of substituted ethylenes. The $\Delta\Delta G^{\ddagger}_{\psi}$ were obtained from eq 2, where

$$\Delta\Delta G^{\ddagger} = \Delta\Delta G^{\ddagger}_{po} + \Delta\Delta G^{\ddagger}_{\psi} \quad (2)$$

$\Delta\Delta G^{\ddagger}_{po}$ is the polar contribution and $\Delta\Delta G^{\ddagger}_{\psi}$ is the resonance contribution to the free energy. The $\Delta\Delta G^{\ddagger}_{po}$ is calculated from the correlation of log k for the olefins bearing substituents which do not conjugate with the double bond.

No systematic examination of electrophilic additions by means of the extended Hammett equation[8] (eq 3) is

$$Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + h \text{ (Hammett equation)} \quad (3)$$

extant in the literature. Rate data taken from the literature for the addition of chlorine, bromine, hydronium ion, trifluoroacetic acid, and mercuric ion were correlated with eq 3. Data used are presented Table I. The sources of most of the substituent constants used are reported in previcus papers of this series;[1,9] substituent constants from other sources are set forth in Table II. In several of the sets studied, the compounds are multiply substituted. Correlations in these sets were made with eq 4 which neglects interaction terms.[10]

$$Q_X = \alpha\Sigma\sigma_{I,X} + \beta\Sigma\sigma_{R,X} + h \quad (4)$$

The effect of substituents on orientation in the addition of BH_3 to the double bond was also studied. In the reaction of BH_3 with a substituted ethylene, the boron may bond to either carbon 1 or carbon 2. The overall rate constants for the reaction is given by

$$k_T = k_1 + k_2 \quad (5)$$

where

$$k_1 = p_1k_T;\ k_2 = p_2k_T \quad (6)$$

The quantities p_1 and p_2 denote the per cent of the product with boron bonded to carbon and carbon 2, respectively. Now, applying the extended Hammett equation (eq 4) to the partial rate constants k_1 and k_2 for the reaction of a substituted ethylene gives eq 7 and 8.

$$\log k_{1,X} = \log p_{1,X}k_T = \alpha_1\sigma_{I,X} + \beta_1\sigma_{R,X} + h_1 \quad (7)$$

$$\log k_{2,X} = \log p_{2,X}k_T = \alpha_2\sigma_{I,X} + \beta_2\sigma_{R,X} + h_2 \quad (8)$$

Subtraction of eq 8 from eq 7 gives

$$\log\left(\frac{k_{1,X}}{k_{2,X}}\right) = \log\left(\frac{p_{1,X}}{p_{2,X}}\right) = (\alpha_1 - \alpha_2)\sigma_{I,X} + (\beta_1 - \beta_2)\sigma_{R,X} + k_1 - k_2 \quad (9)$$

or

$$\log\left(\frac{p_{1,X}}{p_{2,X}}\right) = \alpha'\sigma_{I,X} + \beta'\sigma_{R,X} + h' \quad (10)$$

equivalent to eq 4. The data on orientation in the addition of BH_3 to substituted ethylenes are presented in Table I.

We have also examined nucleophilic addition reactions of substituted olefins. The first attempt to apply a linear free-energy relationship to the reactivity of sub-

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TABLE I

DATA USED IN THE CORRELATIONS

1. Substituted Ethylenes + Chlorine in Acetic Acid at 24° [a] (k_{rel})

$CHCl_2$, 0.60; Br, 0.28; SO_3H, 0.11; CO_2Et, 0.056; CO_2H, 0.018; CCl_3, 0.006; SO_2Me, 0.001; CN, 0.0001

2. Substituted Ethylenes + Chlorine in Aqueous Acetic Acid [b] (k_{rel})

Me, 2.0; H, 1.0; CH_2F, 3.4×10^{-2}; CH_2Cl, 1.9×10^{-2}; CH_2Br, 1.3×10^{-2}; CH_2CN, 2.7×10^{-3}; $CHCl_2$, 2.6×10^{-5}; Br, 1.3×10^{-5}; CCl_3, 2.9×10^{-7}

3. Trans-2'-Substituted Styrenes + Chlorine in Acetic Acid at 24° [a] (k_{rel})

Bz, 61.0; Br, 30.0; 3-$O_2NC_6H_4$, 15.0; CO_2Me, 10.0; CO_2H, 4.9; CHO, 1.8; CN, 0.022; NO_2, 0.020.

4. Substituted Ethylenes + Bromine in Aqueous Perchloric Acid at 25° [c] (k)

CO_2Et, 1.06×10^{-1}; CH_2CN, 440.0; H, 3.9×10^5; CH_2OH, 6.7×10^5; Me, 4.5×10^6; $CH_2NMe_3{}^+Br^-$, 2.8×10^{-1}

5. Substituted Ethylenes with Br_3^- in Aqueous Perchloric Acid at 25° [c] (k)

CO_2Et, 6.7×10^{-2}; $CH_2NMe_3{}^+Br^-$, 9.1×10^{-2}; CH_2CN, 100.0; H, 2.0×10^4; CH_2OH, 6.9×10^4; Me, 3.2×10^5

6. Trans-1,2-Disubstituted Ethylenes + Bromine in Aqueous Perchloric Acid at 25° [c] (k)

CO_2Et, CO_2Et, 3.4×10^{-5}; CO_2Et, Me, 2.76; Cl, CH_2OH, 3.08; Ph, $CH_2NMe_3{}^+Br^-$, 37.0; CO_2Et, Ph, 220.0

7. Trans-1,2-Disubstituted Ethylenes + Br_3^- in Aqueous Perchloric Acid at 25° [c] (k)

CO_2Et, CO_2Et, 3.7×10^{-4}; CO_2Et, Me, 1.04; Cl, CH_2OH, 0.31; Ph, $CH_2NMe_3{}^+Br^-$, 4.8; CO_2Et, Ph, 2.3

8. Substituted Ethylenes + Bromine in Acetic Acid at 24° [a] (k)

Ph, 11,000; Bu, 2000; H, 84.0; CH_2OAc, 10.0; CH_2OBz, 14.0; CH_2Cl, 1.6; CH_2Br, 1.0; CH_2CN, 0.23; Br, 0.0011; CO_2Et, 0.004

9. Trans-2'-Substituted Styrenes + Bromine in Acetic Acid at 24° [a] (k)

CH_2Cl, 77.0; Ph, 18.0; Br, 0.11; CO_2H, 0.019; H, 11,000

10. Substituted Ethylenes + Bromine in MeOH 0.2 M in NaBr at 25° [d] ($\log k$)

H, 1.481; Et, 3.462; Pr, 3.320; Bu, 3.299; *sec*-Bu, 2.966; CH_2-*t*-Bu, 2.539; OEt, 8.54; OAc, 3.36

11. Substituted Ethylenes + Bromine in Acetic Acid + HBr at 24° [a] (k_{rel})

CH_2OBz, 9.0; CH_2Cl, 3.8; CH_2Br, 2.2; Br, 0.012; CO_2H, 0.44

12. Trans-2'-Substituted Styrenes + Br_2 in Acetic Acid + HBr at 24° [a] (k_{rel})

CH_2Cl, 16.0; Ph, 8.0; Br, 0.07; CN, 4.0; NO_2, 1.0

13. 2-Substituted Propenes + H_3O^+ in 29.6% Aqueous Perchloric Acid at 38° [e] (k_{rel})

H, 1.0; CH_2Cl, 1.0; CH_2OMe, 30.0; Ph, 5000; Me, 8000; Et, 10,000; *t*-Bu, 8000

14. 2-Substituted Propenes + Trifluoroacetic Acid in Trifluoroacetic Acid at 25° [f] (k)

H, 4.81; F, 340.0; Cl, 1.70; Br, 0.395

15. Substituted Ethylenes + Mercuric Perchlorate in Water at 25° [g] (k)

H, 5100; Me, 100,000; Et, 80,000; CH_2OH, 1120; CH_2CH_2OH, 8400; $MeCHOHCH_2$, 6100; CH_2Cl, 11.0; CH_2CN, 4.3

16. Orientation in the Reaction $XCH{=}CH_2 + B_2H_6$ in THF at 0° [h] ($\log p_1/p_2$)

Et, 1.195; Ph, 0.6021; $PhCH_2$, 0.9542; $ClCH_2$, 0.1761; Me_3Si, 0.3076; CF_3, −0.4543; $ClCH_2CH_2$, 0.6585; EtO_2CCH_2, 0.6886

21. Rates of Addition of Diglycine Anion to Substituted Ethylenes in H_2O, μ = 1.2; pH = 8.75 at 30° (10^4k_2, M^{-1} sec^{-1}) [i]

CO_2NH_2, 2.00; CO_2Me, 46.0; CN, 13.7; SO_2Me, 90.0

22. Rates of Addition of Glycine Anion to Substituted Ethylenes in H_2O, μ = 1.2; pH = 8.75; 30° (10^4k_2 M^{-1} sec^{-1}) [i]

$CONH_2$, 6.30; $PO(OCH_2CH_2Cl)_2$, 20.9; CO_2Me, 182.0; CN, 50.0; SO_2Me, 306.0; Ac, 4000.0

23. Rates of Addition of ε-Aminocaproic Acid Anion to Substituted Ethylenes in H_2O, μ = 1.2; pH = 8.75, 30° ($10^{-4}k_2$ M^{-1} sec^{-1}) [i]

$CONH_2$, 16.9; CO_2Me, 528.0; CN, 203.0; SO_2Me, 1120.0

24. Rates of Addition of DL-α-Alanine Anion to Substituted Ethylenes in H_2O, μ = 1.2; pH = 8.75; 30° (10^4k_2 M^{-1} sec^{-1}) [i]

$CONH_2$, 3.50; $PO(OCH_2CH_2Cl)_2$, 10.7; CO_2Me, 111; CN, 35.3; Ac, 2280

25. Rates of Addition of Methoxide to Substituted Ethylenes in MeOH at 24° (k_2 l. mol^{-1} min^{-1}) [j]

Ac, 26.4; $EtSO_2$, 2.46; CN, 0.732; CO_2Me, 0.21; EtCO, 14.1

26. Rates of Addition of Morpholine to Substituted Ethylenes in MeOH at 0° (10^4k_2 M^{-1} sec^{-1}) [k]

$PO(OEt)_2$, 0.233; $CONH_2$, 0.561; CN, 14.4; CO_2Me, 32.8; Ts, 187.0; Ac, 3770.0; CHO, 6490.0; Bz, 20,800

27. Rates of Addition of Morpholine to Substituted Ethylenes in Methanol at 30° (10^4k_2 M^{-1} sec^{-1}) [k]

$PO(OEt)_2$, 1.43; $CONH_2$, 3.57; CN, 56.8; CO_2Me, 104.0; Ts, 755; CO_2Ph, 1410.0; Ac, 12,000; CHO, 12,800; Bz, 40.500

28. Rates of Addition of Morpholine to Substituted Ethylenes in MeOH at 45° (10^4 k_2 M^{-1} sec^{-1}) [k]

$PO(OEt)_2$, 33.1; $CONH_2$, 65.1; CN, 106.0; CO_2Me, 162.0; Ts, 1200; CO_2Ph, 2270; Ac, 23.300; CHO, 17,000; Bz, 49,200

[a] P. B. D. de la Mare and R. Bolten, "Electrophilic Additions to Unsaturated Systems," Elsevier, Amsterdam, 1966, p 84. [b] J. R. Shelton and L. H. Lee, *J. Org. Chem.*, **25**, 428 (1960). [c] R. P. Bell and M. Pring, *J. Chem. Soc. B*, 1119 (1966). [d] J. E. Dubois and G. Mouvier, *Tetrahedron Lett.*, 1325 (1963); J. E. Dubois, P. Alcais, G. Barbier, and E. Bienvenue-Goetz, *Bull. Soc. Chim. Fr.*, 2113 (1966). [e] R. W. Taft, Q. N. Report 1960, p 6 (cited in ref *a*). [f] P. E. Peterson and R. J. Bopp, *J. Amer. Chem. Soc.*, **89**, 1283 (1967). [g] J. Halpern and H. B. Tinker, *J. Amer. Chem. Soc.*, **89**, 6427 (1967). [h] H. C. Brown and K. A. Keblys, *J. Amer. Chem. Soc.*, **86**, 1795 (1964). [i] Reference 11. [j] R. N. Rign, G. C. Tesoro, and D. R. Moore, *J. Org. Chem.*, **32**, 1091 (1967). [k] Reference 12; k_{rel} indicates relative reaction rates.

stituted ethylenes undergoing nucleophilic addition is that of Friedman and Wall.[11] These authors proposed the equation

$$\log k_X = P_V + \log k_{CN} \quad (11)$$

where k_X represents the rate constant for the reaction of the substituted ethylene bearing the X substituent with the anion of some amino acid, k_{CN} represents the rate constant for the reaction of acrylonitrile with the same nucleophile, and P_V is a measure of the electrical effect of X relative to that of the cyano group. These authors also reported nearly linear plots of log k_X against $\sigma - \sigma^\circ$ and against σ_R. A plot of log k_X against $\sigma^- - \sigma^\circ$ was said to give only qualitative correlation. Shenhav, Rappoport, and Patai[12] have re-

(11) M. Friedman and J. S. Wall, *J. Org. Chem.*, **31**, 2888 (1966).

(12) H. Shenhav, Z. Rappoport, and S. Patai, *J. Chem. Soc. B*, 469 (1970).

TABLE II
SUBSTITUENT CONSTANTS

X	I	Source	R	Source
CH_2OMe			−0.08	*a*
CH_2OBz	0.15	*b*	−0.05	*c*
$CH_2NMe_3^+Br^-$	0.25	*b*	0.0	*c*
CH_2F	0.18	*b*	−0.04	*c*
$3\text{-}O_2NC_6H_4$	0.19	*d*	−0.01	*e*
CH_2CH_2OH	0	*f*	−0.10	*c*
$MeCHOHCH_2$			−0.13	*c*
CH_2OAc	0.14	*g*	−0.05	*c*, *g*
$CONH_2$			0.09	*h*
$PO(OCH_2CH_2Cl)_2$	0.52	*i*	0.08	*i*
$PO(OEt)_2$	0.52	*j*	0.08	*j*
$EtSO_3$			0.13	*k*
EtCO	0.29	*l*	0.19	*l*
CHO	0.31	*m*	0.14	*n*
CO_2Ph	0.42	*o*	0.14	*o*

[a] Calculated from $\sigma_R = \sigma_p - \sigma_I$ assuming $\sigma_{p,CH_2OMe} = \sigma_{p,CH_2OH}$. [b] Calculated from $\sigma_{I,XCH_2} = 0.3685\sigma_{I,X} - 0.01656$. [c] Calculated from $\sigma_R = \sigma_p - \sigma_I$. σ_p calculated from $\sigma_{p,XCH_2} = 0.5217\sigma_{I,X} - 0.1306$. [d] From pK_a of $3\text{-}O_2NC_6H_4CH_2CO_2H$. [e] From $\sigma_R = \sigma_p - \sigma_I$. [f] From pK_a of $HOCH_2CH_2CH_2CO_2H$. [g] M. Charton, *J. Org. Chem.*, **30**, 3346 (1965). [h] M. Charton, *J. Org. Chem.*, **28**, 3121 (1963). [i] Assumed equal to substituent constants for $PO(OEt)_2$. [j] Calculated from σ_m and σ_p values reported by L. D. Freedman and H. H. Jaffé, *J. Amer. Chem. Soc.*, **77**, 920 (1055). [k] Assumed equal to σ_R for $MeSO_2$. [l] M. Charton, *J. Org. Chem.*, **36**, 266 (1971). [m] Calculated from the equation $\sigma_{I,XCO} = 0.308\sigma_{m,X} + 0.31$. [n] Calculated from the σ_p value reported by K. Bowden and M. J. Shaw, *J. Chem. Soc. B*, 161 (1971). [o] Calculated from σ_m and σ_p values estimated as described in footnote *a*. Other values of σ_I are generally taken from M. Charton, *J. Org. Chem.*, **29**, 1222 (1964). Other values of σ_R are obtained as in footnote *e*, using σ_p values reported by D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).

ported a correlation of the rate constants of the addition of morpholine to substituted ethylenes with the P_V values of Friedman and Wall. They also report a correlation of the rates with the σ_R values where $\rho = 48$. This correlation was limited to substituents with σ_R in the range of 0.10 to 0.15. Sufficient data is extant in the literature for eight sets of nucleophilic addition to substituted ethylenes. The sets studied are reported in Table I. The data were correlated with eq 1 and with the equation

$$Q_X = \alpha\sigma_{I,X} + \beta\sigma^-_{R,X} + h \quad (12)$$

where $\sigma^-_{R,X}$ is defined by

$$\sigma^-_{R,X} = \sigma^-_{p,X} - \sigma_{I,X} \quad (13)$$

using the σ^-_p values reported in the review of Ritchie and Sager.[13] The data have also been correlated with eq 14.

$$Q_X = \beta\sigma_{R,X} + h \quad (14)$$

Results

The results of the correlations are presented in Table III. It should be noted that the magnitude of the multiple correlation coefficient is not the best measure of the goodness of fit of data to an equation with two or more independent variables. For such an equation, the best measure of goodness of fit is the confidence level of the F test for significance of regression. For correlation with an equation having only a single independent variable the confidence level of the "t" test for significance of the regression coefficient of that variable is the best measure of goodness of fit. We consider a confidence level (CL) of >99% to be excellent; 99.0% very good; 97.5–98%, good; 95% fair; 90%, poor; and <90%, not significant. The equation which gives the best correlation is that equation for which the highest confidence level is observed. It is therefore entirely possible to get a more significant correlation with an equation which possesses fewer independent variables than its competitor.

The value for SO_3H was excluded from set 1 as it is uncertain whether or not this group is ionized. The results obtained are excellent. Set 2 also gave an excellent correlation. Set 3 gave good results which were slightly improved by the exclusion of the value for X = Bz (set 3A). Sets 4 and 5 gave good correlation; sets 6 and 7 did not give significant results. Sets 8 and 10 gave excellent correlation; set 9 did not give significant results, perhaps owing to the small size of the set. The value for X = Ph was excluded from sets 8 and 9 as it obviously did not fit. Possibly this compound reacts by a different path. Set 11 gave good results. It is particularly significant that the values of α and β obtained for sets 12 are both significant and differ in sign. If the correlation is meaningful, this suggests a composite substituent effect made up of contributions from two or more steps. Set 13 gave very good correlation. Set 14 did not give significant results, again perhaps owing to the small size of the set. Set 15 gave an excellent correlation as did set 16.

The results for sets 26–28 are all slightly improved by the exclusion of the value for X = CHO. This is most likely due to the uncertainty in the value of σ_R for the formyl group. Of the eight nucleophilic addition sets studied, five gave significant correlation with eq 3. In all of these sets, however, α was not significant. No sets gave significant correlation with eq 12. Best results were obtained for correlations with eq 14; of the eight sets studied, six gave significant correlation with eq 14. The two sets which did not give significant correlation with σ_R had only four points each and encompassed a range of only 0.05 σ unit. Of the six sets which did give significant correlation with eq 14, one gave excellent, one gave very good, three gave good, and one gave poor correlation.

Discussion

Composition of the Electrical Effect.—Previously in this series of papers, the composition of the electrical effect was described by means of the parameter, ϵ, where

$$\epsilon = \beta/\alpha \quad (15)$$

A more useful measure of the composition of the electrical effect may be defined as

$$P_R = \frac{\beta \times 100}{\alpha + \beta} \quad (16)$$

where P_R is the per cent resonance effect. The quantities ϵ and P_R are related to each other by eq 17.

$$P_R = \frac{\epsilon \times 100}{\epsilon + 1} \quad (17)$$

Values of P_R are given in Table IV.

(13) C. D. Ritchie, and W. F. Sager, *Prog. Phys. Org. Chem.*, **2**, 323 (1963).

TABLE III

RESULTS OF CORRELATIONS

Set	α	β	h	R[a]	F[b]	r[c]	s_{estd}[d]	s_α[d]	s_β[d]	s_h[d]	n[d]
1	−9.72	−5.60	2.28	0.980	49.28[g]	0.244	0.369	1.35[h]	1.15[h]	0.601[i]	7
2	−13.5	−3.38	0.912	0.965	40.82[f]	0.378	0.696	1.55[f]	3.71[o]	0.397[l]	9
3	−7.14	−3.02	3.41	0.881	8.672[j]	0.012	0.756	1.79[i]	2.39[o]	0.781[h]	8
3A[r]	−6.22	−4.77	2.94	0.928	12.45[j]	0.121	0.603	1.50[i]	2.10[l]	0.667[i]	7
4	−22.4	2.29	6.10	0.974	28.15[j]	0.838	0.974	4.23[k]	10.5[q]	0.886[h]	6
5	−19.1	0.832	4.86	0.964	19.98[j]	0.838	1.01	5.43[k]	10.9[q]	0.920[i]	6
6	−10.7	−5.82	4.70	0.857	2.762[m]	0.376	1.94	6.85[o]	5.54[o]	3.33[o]	5
7	−8.35	−2.73	3.32	0.837	2.337[m]	0.376	1.43	5.05[o]	4.08[p]	2.45[o]	5
8	−13.0	−3.56	2.25	0.981	78.65[f]	0.133	0.440	1.04[f]	1.75[l]	0.238[f]	9
9	−9.76	−4.53	2.37	0.931	3.238[m]	0.178	1.09	3.93[o]	4.63[p]	1.15[o]	4
10	0.328	−13.2	1.64	0.973	44.79[f]	0.477	0.569	1.35[q]	1.61[f]	0.292[h]	8
11	−7.49	2.20	1.93	0.990	48.46[j]	0.330	0.228	0.895[i]	1.03[n]	0.239[i]	5
12	−3.72	6.80	2.01	0.990	48.64[j]	0.512	0.187	0.423[i]	0.816[i]	0.201[h]	5
13	−4.32	−32.9	−0.158	0.959	22.96[h]	0.447	0.651	3.46[q]	6.08[o]	0.587[h]	7
14	−8.48	−13.7	0.672	0.985	16.46[m]	0.879	0.375	1.88[n]	2.41[n]	0.375[o]	4
15	−18.3	−0.554	0.835	0.995	262.7[f]	0.694	0.187	1.12[f]	1.93[p]	0.174[h]	8
16	−1.26	−3.88	0.444	0.948	220.4[g]	0.428	0.192	0.492[l]	0.875[h]	0.0990[h]	8
21A	1.79	19.2	−1.45	0.797	0.873[m]	0.319	0.758	2.81[p]	2.14[p]	2.14[p]	4
21B	1.90	4.31	−1.17	0.678	0.424[m]	0.418	0.924	3.58[p]	9.33[p]	3.15[p]	4
21C		23.5	−1.09	0.699			0.635		17.0[o]		4
22A	1.70	19.4	−0.940	0.921	8.437[l]	0.376	0.495	1.61[o]	4.76[k]	1.05[o]	6
22B	0.995	8.14	−1.58	0.848	2.568[m]	0.193	0.773	2.49[p]	3.59[m]	1.98[p]	5
22C		17.5	0.0124	0.891			0.501		0.448[i]		6
23A	2.38	17.8	−0.514	0.794	0.855[m]	0.319	0.834	3.10[p]	23.5[p]	2.35[q]	4
23B	2.54	3.63	−0.140	0.698	0.476[m]	0.418	0.983	3.80[p]	9.93[p]	3.36[q]	4
23C		23.6	−0.0337	0.643			0.744		1.99[o]		4
24A	2.25	20.2	−1.45	0.911	4.862[m]	0.538	0.632	2.66[o]	6.76[l]	1.63[o]	5
24B	2.71	9.26	−2.81	0.865	1.491[m]	0.465	1.02	4.63[p]	5.41[o]	3.35[p]	4
24C		17.1	−0.211	0.877			0.601		5.42[l]		5
25A	2.13	18.5	−3.09	0.978	21.48[k]	0.674	0.260	1.13[n]	3.13[k]	0.848[l]	5
25B	0.895	7.53	−3.35	0.957	5.431[m]	0.426	0.450	1.83[p]	2.38[m]	1.57[o]	4
25C		14.5	−1.63	0.936			0.355		3.16[i]		5
26A$_1$	1.14	35.0	−2.81	0.841	6.044[l]	0.552	1.19	4.09[p]	11.5[k]	2.71[o]	8
26A$_2$	2.30	35.0	−3.47	0.874	6.489[l]	0.540	1.09	3.85[p]	10.6[k]	2.53[o]	7
26B	2.21	7.94	−2.60	0.882	3.505[m]	0.280	1.14	4.80[p]	3.02[n]	2.61[o]	5
26C$_1$		33.2	−2.14	0.838			1.09		8.82[i]		8
26C$_2$		31.6	−2.13	0.862			1.02		8.30[i]		7
27A$_1$	1.28	32.7	−2.02	0.861	8.576[k]	0.538	0.932	3.16[p]	8.84[i]	2.10[i]	9
27A$_2$	2.33	32.9	−2.62	0.892	9.699[j]	0.528	0.847	2.95[o]	8.04[h]	1.95[o]	8
27B	1.71	7.13	−1.49	0.877	3.337[m]	0.280	1.06	4.43[p]	2.78[n]	2.41[p]	5
27C$_1$		30.7	−1.27	0.857			0.874		6.99[h]		9
27C$_2$		29.6	−1.26	0.877			0.820		6.61[h]		8
28A$_1$	0.0555	25.9	−0.113	0.912	14.87[h]	0.538	0.568	1.93[q]	5.40[h]	1.28[q]	9
28A$_2$	0.817	25.1	−0.554	0.944	20.52[g]	0.528	0.464	1.62[p]	4.41[h]	1.07[p]	8
28B	−0.434	5.77	0.365	0.918	5.345[m]	0.280	0.707	2.97[q]	1.86[l]	1.61[q]	5
28C$_1$		24.8	−0.0806	0.912			0.526		4.21[h]		9
28C$_2$		23.9	−0.0758	0.941			0.435		3.50[f]		8

[a] Multiple correlation coefficient. [b] F test for significance of regression. [c] Partial correlation coefficient of σ_I on σ_R. [d] Standard deviation of the estimate, α, β, and h. [e] Number of points in the set. [f] 99.9% confidence level (CL). [g] 99.5% CL. [h] 99.0% CL. [i] 98.0% CL. [j] 97.5% CL. [k] 95% CL. [l] 90% CL. [m] <90% CL. [n] 80% CL. [o] 50% CL. [p] 20% CL. [q] <20% CL. [r] Sets labeled A, B, and C were correlated with eq 3, 12, and 14, respectively.

TABLE IV

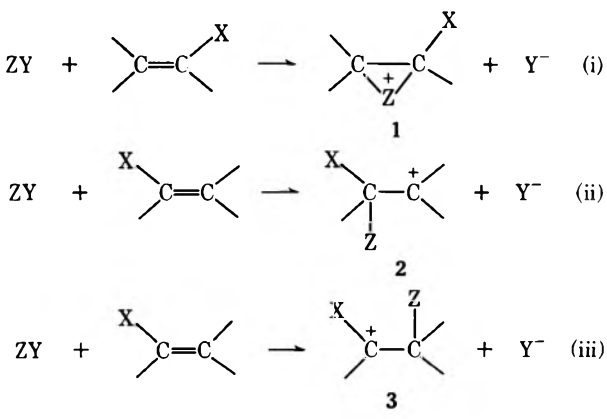
VALUES OF P_R[a]

Set	P_R	Set	P_R	Set	P_R	Set	P_R
1	37	5	4	9	*c*	13	*e*
2	*b*	6	*d*	10	*e*	14	*d*
3	43	7	*d*	11	*b*	15	*b*
4	*c*	8	21	12	*d*	16	76

[a] For sets with $P_R > 50$, β is predominant, whereas, for sets with $P_R < 50$, α is predominant. [b] β is not significant for this set. [c] σ_I is a function of σ_R for this set. [d] Correlation is not significant for this set. [e] α is not significant for this set.

Mechanism of Electrophilic Addition.—In the majority of the sets studied (sets 1–5, 8, 11, 15) a large significant value of α was obtained, while β was small and in some cases not significant. Thus two major classes of electrophilic addition to olefins seem to exist in so far as substituent effects are concerned. We believe that this behavior may be accounted for in terms of the addition mechanism. The rate-determining step in the electrophilic addition to the double bond is the formation of an intermediate which may be either bridged or a free carbonium ion.[14] Thus i–iii obtain. Those sets for which β is predominant are the sets which are most likely to give rise to the free carbonium ion, **3**, as the substituents in these sets are all donors by resonance. This can readily be seen from the σ_R

(14) While structures **1**, **2**, and **3** may well represent points in a spectrum of intermediate type, it is certainly conceivable that for a given set of substrates the intermediate is closest to one of these species, and they are therefore very useful for purposes of discussion.



values of these substituents. Those sets for which α is predominant may be accounted for in terms of the formation of intermediates **1** or **2**. Sets 1, 3A, and 8 gave significant although small values of β. It is difficult to account for this in terms of intermediate **2**. The results can, however, be accounted for in terms of intermediate **1** if the species resembles other three-membered rings in behavior. Sets 2, 4, 5, 8, and 11 include both donor and acceptor substituents. The succcssful correlation of these sets suggests that the same mechanism operates throughout the set. Then we may exclude free carbonium ion formation in these sets as the donor-substituted compounds would lead to **3** and the acceptor-substituted compounds would lead to **2** if free carbonium ions were to form. As substituent effects are not the same for **2** and **3**, this would result in a lack of correlation with eq 3. Then we conclude that in these sets the addition must proceed through the formation of the bridged intermediate **1**. Since all of the substituents in set 15 are donors by resonance with the exception of X = H, if a free carbonium ion were to form, it would be expected to be **3**. This intermediate should show a large and significant β value, however. We conclude therefore that in set 15 the reaction again proceeds by way of the bridged intermediate, **1**. The results obtained show that correlations with the extended Hammett equation are of use in describing the mechanism of the electrophilic addition to the double bond.

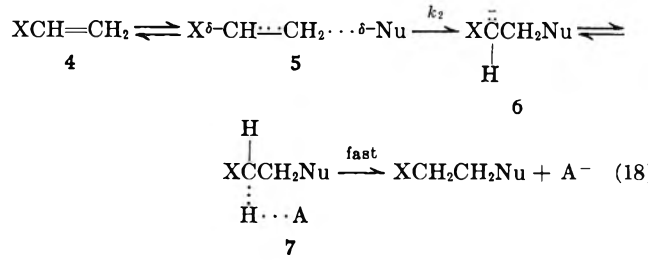
Magnitude of the Electrical Effect in Electrophilic Addition.—The β values observed for the sets in which α is predominant are smaller than the β values observed for substituent effects on dienophiles in the Diels–Alder reaction (the latter values must be corrected for multiple substitution by dividing by two). The β values observed for the sets in which β is predominant are large, in accordance with a mechanism proceeding *via* intermediate **3**. The α values obtained for sets in which α is predominant are also large.

Multiply Substituted Sets in Electrophilic Addition.—The failure to obtain significant correlation in sets 6 and 7 cannot be attributed to a change in mechanism. A comparison of the substituents in sets 6 and 7 with those present in sets 4 and 5 suggests that, if more than one mechanism occurs in sets 6 and 7, then it should also occur in sets 4 and 5. Since sets 4 and 5 are successfully correlated with eq 3, we may reject the multiple mechanism hypothesis. The lack of correlation may possibly be due to the neglect of interaction terms in the use of eq 4 or perhaps to steric factors.

Orientation in Electrophilic Addition.—The results of correlation with eq 10 show that orientation in electrophilic addition can be successfully represented by the extended Hammett equation. It would seem that orientation in the addition of BH_3 to substituted ethylenes is primarily dependent upon the delocalized electrical effect. There is one surprising point concerning the results. For that member of the set for which X = H, carbon 1 is equivalent to carbon 2 and therefore $p_1 = p_2$. Then $\log (p_1/p_2)_H = 0$ and therefore h' should be equal to zero. The value actually obtained is significantly different from zero. This may possibly be due to a constant steric effect.

Nucleophilic Addition.—Obviously, the electrical effect in nucleophilic addition to the double bond is almost purely a resonance effect. In magnitude the electrical effect is very large. The values of β obtained range from 14 to 32. This is comparable to the range of β observed for those electrophilic addition sets for which β was predominant, the range in that case being -13 to -33.[11]

The results are in accord with a mechanism involving the formation of a carbanion, **6**, by a rate-determining step (eq 18). The carbanion, **6**, in which



the substituent X is directly attached to the carbon bearing the negative charge, would be expected to show a large degree of resonance stabilization of the negative charge. Thus, a large positive value of β for this reaction is in agreement with the formation of **6** by a transition state, **5**, which is closer to **6** than to **4**. If the transition state were closer to **4** than to **6**, the resonance effect would not be predominant, and β would be much smaller.

The β values are a function of temperature as is shown by the results for sets $26C_2$, $27C_2$, and $28C_2$. Contrary to the literature[15] however, β is not linear in $1/T$. The β values ought to be dependent on both solvent and nucleophile. Thus, in the case of the nucleophile, let the reactivity as a function of nucleophile be given by the equation

$$Q_{Nu} = aN_{Nu} + h \tag{19}$$

where N is a parameter characteristic of the nucleophile reactivity. When the nucleophile is held constant, and the substituent in the substituted ethylene is varied, the data may be represented by eq 20 where h_{Nu} repre-

$$Q_{X,Nu} = \beta_{Nu}\sigma_{R,X} + h_{Nu} \tag{20}$$

sents the reactivity of the unsubstituted compound (ethylene itself). Then from eq 19

$$h_{Nu} = aN_{Nu} + h \tag{21}$$

and

$$Q_{X,Nu} = \beta_{Nu}\sigma_{R,X} + aN_{Nu} + h \tag{22}$$

(15) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

According to Miller,[10] the quantity $Q_{X,Nu}$ can be written as eq 23 where $\chi\sigma_{R,X}N_{Nu}$ is the so-called interaction term.

$$Q_{X,Nu} = \beta\sigma_{R,X} + aN_{Nu} + \chi\sigma_{R,X}N_{Nu} + h \quad (23)$$

Setting eq 22 equal to eq 23 and dividing through by $\sigma_{R,X}$ gives eq 24 which predicts that the slopes of the

$$\beta_{Nu} = \chi N_{Nu} + \beta \quad (24)$$

line obtained from correlation with eq 17 will be a linear function of the nucleophilicity parameter, N. The same type of equation can be derived from the solvent variation. Thus,

$$\beta_{Sv} = \chi S_{Sv} + \beta \quad (25)$$

Unfortunately, the data available here do not permit a test of eq 24 and 25.

The results obtained would undoubtedly be much improved if a wider range of σ_R values could be studied. The largest range of σ_R studied in this work encompassed only 0.14 σ units. It is unlikely that a greater range of σ will be studied as no substituent with $\sigma_R > 0.21$ is known, and it is unlikely that a substituent with $\sigma_R < 0.07$ would react at a measurable rate.

It is interesting to note that, although σ_R^- values might have been expected to be the substituent constants most applicable to reactions involving carbanions, correlations with eq 12 are generally inferior to correlations with eq 3 in which σ_R constants were used. This is partly due to the fact that values of σ_R^- were not available for all substituents, and therefore in several cases all the members of the set could not be correlated by eq 12. Nevertheless, eq 12 is not successful in correlating this data. Thus no attempt was made to correlate data with the equation

$$Q_X = \beta\sigma^-_{R,X} + h \quad (26)$$

Why Increasing Concentrations of Ethylenediamine Cause the Rate of Exchange of Isobutyraldehyde-2-*d* to Rise, Then Fall, and Then Rise Again[1a,b]

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First-order rate constants for the deuterium exchange of about 0.06 M isobutyraldehyde-2-*d* in aqueous solution around pH 8.5 increase with increasing concentrations of added ethylenediamine and reach a maximum at diamine concentrations around 0.03 M. They then decrease, pass through a minimum around diamine concentrations of 0.1 M, and finally increase again. This behavior is explained in terms of the transformation of most of the limiting reagent to 2-isopropylimidazolidine (or its conjugate acid), which then catalyzes the exchange of remaining aldehyde. Exchange by this pathway is fastest when half the aldehyde has been transformed to imidazolidine. At higher concentrations of diamine most of the exchange arises from attack of the various bases present on the small amounts of iminium ions, such as $Me_2CDCH{=}NHCH_2CH_2NH_2^+$, which are present in equilibrium with the imidazolidine. Quantitative treatment of the data gives reasonable agreement with the experimental rate constants. A few measurements using N-methylethylenediamine also show a rate maximum and minimum, but N,N'-dimethylethylenediamine, which gives a considerably less basic and more hindered imidazolidine, shows no extrema.

In searching for bifunctional catalysts for the dedeuteration of isobutyraldehyde-2-*d*,[1b,2,3] it was observed that the rate of dedeuteration of ~0.06 M isobutyraldehyde-2-*d* in the presence of ethylenediamine around pH 8.38 at first increased, then decreased, and then increased again as the concentration of diamine was increased from zero to about 0.5 M. We developed a hypothesis, which included the formation of 2-isopropylimidazolidine and its action as a basic catalyst, to explain these results. To test this hypothesis (and for other reasons), the equilibrium constant for the formation of 2-isopropylimidazolidine from isobutyraldehyde and ethylenediamine was measured and the basicity constant of the imidazolidine was determined.[4] The way in which these results and additional kinetic measurements support our hypothesis will be described in the present paper.

Results

The kinetics of the dedeuteration of isobutyraldehyde-2-*d* in the presence of ethylenediamine at 35° were studied at various concentrations and various pH's. The reaction was followed in the manner described previously[5,6] by acidifying the reaction mixture to stop the reaction (and to hydrolyze any imines, imidazolidines, etc., to aldehyde), extracting the aldehyde, and making proton magnetic resonance measurements to determine the extent of deuteration of the aldehyde. Satisfactory first-order rate constants were obtained in the various runs and their values are collected in Table I. Rate constants for the runs at pH 8.37 ± 0.14 using 0.060 ± 0.007 M isobutyraldehyde-2-*d* are plotted as open circles against the concentration of ethylene-

(1) (a) This investigation was supported in part by Public Health Service Grants AM 06829 and 10378 from the National Institute of Arthritis and Metabolic Diseases and GM 18593 from the National Institute of General Medical Sciences. Abstracted in part from the Ph.D. Dissertation of K. W. Narducy, The Ohio State University, 1971. Direct correspondence to The Ohio State University. Part XIV in the series "Catalysis of α-Hydrogen Exchange." (b) For part XIII see J. Hine, E. F. Glod, R. E. Notari, F. E. Rogers, and F. C. Schmalstieg, *J. Amer. Chem. Soc.*, **95**, 2537 (1973). (c) NIH Predoctoral Fellow (No. F01 GM 41963), 1968–1971.

(2) J. Hine, F. E. Rogers, and R. E. Notari, *J. Amer. Chem. Soc.*, **90**, 3279 (1968).

(3) J. Hine, B. C. Menon, J. Mulders, and R. L. Flachskam, Jr., *J. Org. Chem.*, **34**, 4083 (1969).

(4) J. Hine and K. W. Narducy, *J. Amer. Chem. Soc.*, in press.

(5) J. Hine, J. G. Houston, J. H. Jensen, and J. Mulders, *ibid.*, **87**, 5050 (1965).

(6) J. Hine, B. C. Menon, J. H. Jensen, and J. Mulders, *ibid.*, **88**, 3367 (1966).

TABLE I

RATE OF DEDEUTERATION OF ISOBUTYRALDEHYDE-2-d IN THE PRESENCE OF ETHYLENEDIAMINE IN WATER AT 35°

$[Me_2CDCHO]_0$,[a] M	[Diamine],[a] M	pH[b]	10^6k, sec^{-1}
0.044	0.285	8.33	2.0
0.052	0.293	8.32	2.2
0.053	0.0127	8.72[c]	3.4
0.053	0.0252	8.76[c]	5.1
0.053	0.050	8.49[c]	2.0
0.053	0.050	8.67[c]	3.5
0.053	0.073	8.59[c]	2.2
0.053	0.098	8.51[c]	1.20
0.053	0.100	8.67[c]	1.96
0.053	0.149	8.76[c]	2.3
0.053	0.195	8.50[c]	2.0
0.053	0.250	8.70[c]	2.7
0.067	0.239	8.24	1.73
0.067	0.335	8.31	2.6
0.067	0.382	8.33	3.2
0.067	0.430	8.35	3.4
0.067	0.478	8.36	4.2
0.071	0.312	8.29	2.4
0.088	0.238	8.19	2.1
0.088	0.329	8.27	2.6
0.107	0.284	8.19	2.2
0.107	0.427	8.29	3.5
0.216	0.796	9.63	7.2
0.216	0.977	9.84	7.2
0.216	1.16	9.99	7.2

[a] Total concentration.[7] [b] Calculated unless otherwise noted. [c] Observed.

diamine in Figure 1.[7] Rate constants for the runs at PH 8.68 ± 0.09 using 0.053 *M* isobutyraldehyde-*2-d* are plotted as solid circles in the same figure. In each case the rate is seen to pass through a maximum at a diamine concentration around 0.03 *M*, then a minimum around 0.1 *M*, and then to increase with increasing concentrations of diamine.

Less detailed studies were made of the catalytic activities of *N*-methylethylenediamine and *N,N'*-dimethylethylenediamine in the exchange of 0.053 *M* isobutyraldehyde-*2d*. Rate constants obtained with the *N*-methyl compound are listed in Table II and those

TABLE II

RATE OF DEDEUTERATION OF 0.053 *M* ISOBUTYRALDEHYDE-*2-d* IN THE PRESENCE OF *N*-METHYLETHYLENEDIAMINE IN WATER AT 35°

[Diamine],[a] M	pH[b]	10^6k, sec^{-1}
0.095	8.50	2.9
0.097	8.48	3.0
0.199	8.55	1.5
0.199	8.52	2.1
0.400	8.49	2.6
0.484	8.54	2.7

[a] Total concentration.[7] [b] Observed.

for the *N,N'*-dimethyl compound in Table III. The plots in Figure 2 show that the *N*-methyl compound at pH 8.51 ± 0.04 gives a maximum and then a minimum, but that with the *N,N'*-dimethyl compound at pH 8.66 ± 0.07 it is not clear that there are any extrema.

(7) The concentrations given are "total" concentrations, without regard to how much of the compounds is actually transformed to imidazolidines, imines, etc., or to the state of protonation of the bases in the reaction mixtures.

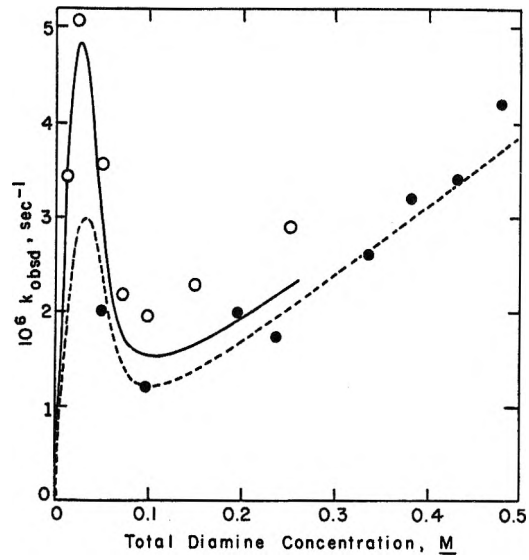


Figure 1.—Rate constants for the dedeuteration of isobutyraldehyde-*2-d* in water at 35° plotted against ethylenediamine concentration: ○, at pH 8.68 ± 0.09 and 0.053 *M* aldehyde; ●, at pH 8.37 ± 0.14 and 0.060 ± 0.007 *M* aldehyde. Lines constructed as described in text.

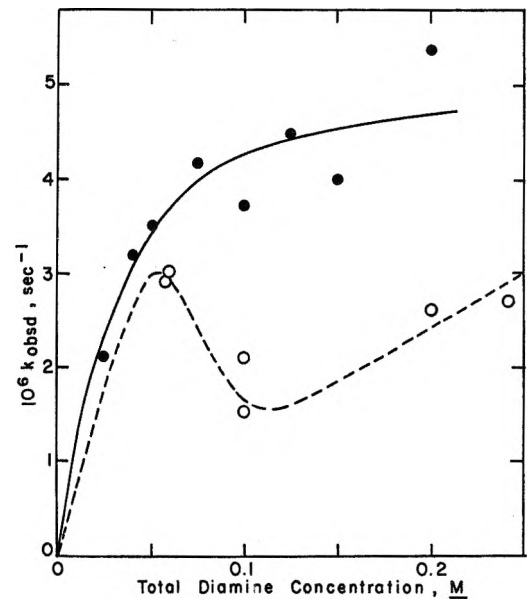


Figure 2.—Rate constants for the dedeuteration of isobutyraldehyde-*2-d* at initial concentrations of 0.053 *M* in water at 35°: ○, at pH 8.51 ± 0.04 in the presence of *N*-methylethylenediamine; ●, at pH 8.66 ± 0.07 in the presence of *N,N'*-dimethylethylenediamine. Lines constructed as described in text.

TABLE III

RATE OF DEDEUTERATION OF 0.053 *M* ISOBUTYRALDEHYDE-*2-d* IN THE PRESENCE OF *N,N'*-DIMETHYLETHYLENEDIAMINE IN WATER AT 35°[a]

[Diamine], M	pH[b]	10^6k, sec^{-1}
0.025	8.60	2.1
0.040	8.63	3.2
0.050	8.63	3.5
0.075	8.64	4.2
0.100	8.66	3.7
0.125	8.67	4.5
0.150	8.67	4.0
0.200	8.73	5.4

[a] Total concentration.[7] [b] Calculated.

Discussion

We hypothesized that the formation of imidazolidines was very important in influencing the rate of exchange of isobutyraldehyde-*2-d* in the presence of ethylenediamine and some of its derivatives. Equilibrium constants for the formation of 2-isopropylimidazolidine are so large[4] that at reagent concentrations above 0.001 *M*, isobutyraldehyde and ethylenediamine react completely enough to transform most of the limiting reagent to the imidazolidine. Thus, when small amounts of diamine are added to aldehyde in the concentrations used in our kinetic runs, the diamine is transformed largely to the imidazolidine, which is the principal basic catalyst that acts on the remaining aldehyde. This component of the total reaction rate will reach a maximum (for a given pH and given aldehyde concentration) when half the aldehyde has been transformed to imidazolidine. In the presence of excess diamine the concentration of free aldehyde will be reduced to such a a low level that exchange *via* attack of imidazolidine on free aldehyde will be much less important. Exchange will also be taking place by attack of bases on iminium ions (such as $Me_2CDCH{=}NHCH_2CH_2NH_2^+$) that are present, and the rate of such exchange will increase monotonically with increasing diamine concentration.

Let us test this hypothesis by analyzing the rate data in terms of the suggested reaction mechanism. The rate constants obtained may be compared with values reported for somewhat similar processes in cases where a smaller number of possibilities made the interpretation of the kinetic data more straightforward. Exchange is assumed to take place entirely by the rate-controlling attack of various bases on the deuterated aldehyde (AD) or on one of the deuterated iminium ions, $Me_2CDCH{=}NHCH_2CH_2NH_2^+$ ($HDIm^+$) and $Me_2CDCH{=}NHCH_2CH_2NH_3^{2+}$ ($HDImH^{2+}$), present in the solution, as indicated in eq 1, in which k is a rate

$$v = \sum_i k_{B_i}[B_i][AD] + \sum_i k'_{B_i}[B_i][HDIm^+] + \sum_i k''_{B_i}[B_i][HDImH^{2+}] \quad (1)$$

constant for attack on aldehyde, k' is for attack on the iminium ion $HDIm^+$, and k'' is for attack on the doubly charged iminium ion $HDImH^{2+}$. Secondary deuterium kinetic isotope effects and equilibrium isotope effects will be neglected, so that the equilibrium constant for formation of an imidazolidine or the rate constant for basic catalysis by an imidazolidine, for example, will be independent of whether there is a deuterium atom in the 2-isopropyl substituent of the imidazolidine or not. Since the observed rate constants were calculated in terms of $[AD]_t$, the total concentration of isobutyraldehyde-*2-d* in all forms, as shown in eq 2, we should transform eq 1 into such terms also.

$$v = k_{obsd}[AD]_t \quad (2)$$

In the paper[4] on equilibria the concentrations of imines and iminium ions are estimated to be no more than about 3% of those of the imidazolidine and imidazolidinium ions. Therefore we shall approximate $[AD]_t$ as shown in eq 3, in which Imid and $HImid^+$

$$[AD]_t = [AD] + [Imid] + [HImid^+] \quad (3)$$

are the imidazolidine and imidazolidinium ion, respectively.[8] The equilibrium constant K_{app} was defined in the paper[4] on equilibria as shown in eq 4, in which

$$K_{app} = \frac{[Imid] + [HImid^+]}{[i\text{-PrCHO}][Da]_t} \quad (4)$$

i-PrCHO refers to both free and hydrated aldehyde and $[Da]_t$ is the concentration of diamine in all states of protonation. From the preceding, [AD] may be expressed in terms of $[AD]_t$ as shown in eq 5, in which

$$[AD] = \frac{[AD]_t}{1 + K_{app}[Da]_t} = f_A[AD]_t \quad (5)$$

f_A is the fraction of the aldehyde originally added that is present in the free or hydrated form. If the equilibrium constants K_I and K_{IH} for the formation of the singly and doubly charged iminium ions, respectively, are defined as shown in eq 6 and 7, then $[HDIm^+]$

$$K_I = \frac{[i\text{-PrCH}{=}\overset{+}{N}HCH_2CH_2NH_2]}{[i\text{-PrCHO}][DaH^+]} \quad (6)$$

$$K_{IH} = \frac{[i\text{-PrCH}{=}\overset{+}{N}HCH_2CH_2NH_3^+]}{[i\text{-PrCHO}][DaH_2^{2+}]} \quad (7)$$

and $[HDImH^{2+}]$ may be expressed as shown in eq 8

$$[HDIm^+] = K_I[AD][DaH^+] \quad (8)$$

and 9. Substitution of these equations, which are

$$[HDImH^{2+}] = K_{IH}[AD][DaH_2^{2+}] \quad (9)$$

based on the well-founded assumption that the various equilibria concerned are established rapidly relative to the deuterium exchange reaction, into eq 1 gives eq 10.

$$v = \left(\sum_i k_{B_i}[B_i] + \sum_i k'_{B_i}[B_i]K_I[DaH^+] + \sum_i k''_{B_i}[B_i]K_{IH}[DaH_2^{2+}]\right) f_A[AD]_t \quad (10)$$

The bases from which basic catalysis might be expected are water, hydroxide ion, unprotonated diamine (Da), monoprotonated diamine, imidazolidine, imidazolidinium ion, the iminium ion *i*-$PrCH{=}NHCH_2CH_2NH_2^+$, and the imines *i*-$PrCH{=}NCH_2CH_2NH_2$ and *i*-$PrCH{=}NCH_2CH_2NH_3^+$. The known catalysis constant for water[5] shows that catalysis by attack of water on aldehyde would contribute only about 0.5% to reaction *via* attack on the aldehyde at the lowest diamine concentration used. Because of this inability of water to compete with the other bases in the solution, exchange *via* attack of water on the iminium ions was neglected. The imidazolidinium ion and the iminium ion should be too weakly basic (and the latter's concentration should be too low) for significant amounts of catalysis. Since no basic catalysis by imine was observed in runs using methylamine, where the imine was the most abundant nitrogen base present,[6] we have neglected catalysis by imine nitrogen atoms in the present case, where the relative concentration of imines is much lower. Significant amounts of catalysis by the primary amino group of the uncharged imine seem unlikely in view of its relatively low concentration and the fact that primary amines are not particularly effec-

(8) Since nothing is gained in the present case by treating the aldehyde hydrate as a separate species, we shall define [AD] as the concentration of the deuterated aldehyde in both the free and hydrated form. This is analogous to the definitions of aldehyde concentrations used in calculating the various rate and equilibrium constants that we shall be using.

tive catalysts.[9,10] In a kinetic analysis of the values of k_{obsd} such catalysis by the imine would be indistinguishable from catalysis by its tautomer, the imidazolidine.

Increases in the diamine concentration at a given pH bring about decreases in the concentration of aldehyde and increases in the concentrations of iminium ions. For this reason the fraction of the reaction that proceeds through the aldehyde decreases as the concentration of diamine increases. The fraction of reaction involving the base hydroxide ion must also decrease with increasing concentration of diamine, since the hydroxide ion concentration remains constant, and the concentration of its competitors, the imidazolidine and the unprotonated and monoprotonated diamine, increases. These changes provide reasons for neglecting attack of hydroxide ions on the iminium ions, even though we do allow for attack of hydroxide ions on the aldehyde.

Neglect of the bases indicated and combination of eq 2 with eq 10 gives eq 11, in which the subscripts

$$k_{obsd} = f_A\{k_h[OH^-] + k_i[Imid] + k_d[Da] + k_{dh}[DaH^+] + (k'_i[Imid] + k'_d[Da] + k'_{dh}[DaH^+])K_I[DaH^+] + (k''_i[Imid] + k''_d[Da] + k''_{dh}[DaH^+])K_{IH}[DaH_2^{2+}]\} \quad (11)$$

h, i, d, and dh refer to the bases hydroxide ion, imidazolidine, unprotonated diamine, and monoprotonated diamine, respectively. Since we have the equilibrium constants and acidity constants with which to calculate f_A and the concentrations of the five species shown, and since k_h is known, there are nine unknowns (k_i, k_d, k_{dh}, k'_iK_I, k'_dK_I, $k'_{dh}K_I$, k''_iK_{IH}, k''_dK_{IH}, and $k''_{dh}K_{IH}$) in eq 11. We did not vary the concentrations of all the participating species sufficiently to permit the reliable determination of all these constants. In fact, because of various concentration interdependencies and for other reasons it is not clear that such variation would be possible. It is therefore not surprising that an unrestricted least squares treatment of the data in Table I did not give a plausible set of values for these unknowns.[11] For this reason certain restrictions were introduced. The rate constants for attack of the primary amines Da and DaH^+ on isobutyraldehyde-2-*d* were assumed to fall on a Brønsted line of slope 0.5 with the rate constant for attack by methylamine, the only other primary amine whose reactivity has been studied. (Values of 0.49 and 0.53 for the Brønsted β have been found for 3- and 4-substituted pyridines and phenoxide ions, respectively.[5]) Using the estimate[10,12] that the k_m term observed using methylamine buffers[6] is about 90% owing to attack of amine on deuterioaldehyde gives a rate constant of $2.7 \times 10^{-3}\ M^{-1}$ sec^{-1} for methylamine, from which values of 1.1×10^{-3} and $3.0 \times 10^{-5}\ M^{-1}$ sec^{-1} may be calculated for k_d and k_{dh}, respectively. Since the *N*-methyliminium ion of isobutyraldehyde-2-*d* has been found to be only 84% as selective as the aldehyde toward attack by various bases,[10] we have assumed that this is also true for the iminium ions encountered in the present case. These assumptions give eq 12, in which there are only three unknowns. Least squares treatment of the data in Table I gave the values $1.45 \times 10^{-3}\ M^{-1}$ sec^{-1}, $0.043\ M^{-2}$ sec^{-1}, and $0.50\ M^{-2}$ sec^{-1} for k_i, k'_iK_I, and k''_iK_{IH}, respectively. These values seem plausible.

$$k_{obsd} - f_Ak_h[OH^-] = f_A\{k_i[Imid] + 0.0011[Da] + 0.00003[DaH^+] + ([Imid] + (0.0011/k_i)^{0.84}[Da] + (0.00003/k_i)^{0.84}[DaH^+])k'_iK_I[DaH^+] + ([Imid] + (0.0011/k_i)^{0.84}[Da] + (0.00003/k_i)^{0.84}[DaH^+])k''_iK_{IH}[DaH_2^{2+}]\} \quad (12)$$

The value of k_i corresponds to 2-isopropylimidazolidine attacking isobutyraldehyde-2-*d* 30% more rapidly than does ethylenediamine (according to our estimated rate constant), although the latter amine is about three times as basic. However, secondary amines (if not too hindered) are known to be better catalysts than primary amines of similar basicity.[9] Our k_i is too small by a factor of about two to fall on a Brønsted plot of the points for piperidine, piperazine, and morpholine,[9] suggesting that 2-isopropylimidazolidine is somewhat more hindered than these other secondary amines.

From a plot of log k_B *vs.* log k'_BK_I in the case where k'_B is the rate constant for attack of base on and K_I is the equilibrium constant for formation of the *N*-methyliminium ion of isobutyraldehyde-2-*d*,[10] a value of $0.013\ M^{-2}$ sec^{-1} would be calculated for k'_iK_I if it referred to the *N*-methyliminium ion. Since k'_BK_I for a given base has been found to increase with increasing acidity of the primary ammonium ion from which the iminium ion is formed,[13] a larger value than this would be expected for our k'_iK_I, which refers to the iminium ion formed from monoprotonated ethylenediamine, and a still larger value would be expected for k''_iK_{IH}, which refers to the iminium ion formed from diprotonated ethylenediamine. The values we have obtained are in agreement with these expectations.

From the constants obtained using eq 12, the observed rate constants may be calculated with a standard deviation of 13% and an average deviation of 10%. These constants, a pH of 8.68, and an aldehyde concentration of 0.053 *M* were used to calculate the solid curve in Figure 1, and with a pH of 8.37 and an aldehyde concentration of 0.060 *M* they were used to calculate the dashed curve. Part of the deviations of the points from the respective lines arises from the fact that most points refer to a slightly different set of conditions from those from which the lines were calculated.

In eq 12 all the rate constants were taken as being independent of the ionic strength. Two of these constants, k'_{dh} and k''_{dh}, govern reactions between ions. The data were also treated by using the Davies equation[14] (which takes the form of eq 13 at 35°) to calculate

$$\log \gamma = -0.52Z^2\left(\frac{\sqrt{\mu}}{1+\sqrt{\mu}} - 0.2\,\mu\right) \quad (13)$$

activity coefficients and using the Brønsted method[15] to calculate the ionic strength effect on the rate con-

(9) J. Hine and J. Mulders, *J. Org. Chem.*, **32**, 2200 (1967).

(10) J. Hine, J. Mulders, J. G. Houston, and J. P. Idoux, *ibid.*, **32**, 2205 (1967).

(11) Some of the values were negative. If the computer program was modified to prohibit negative values, some values were zero and some of the nonzero values had implausible relative magnitudes. Furthermore, some of the values could be changed greatly (provided others were also) with very little effect on the sum of the squares of the deviations from the k_{obsd} values.

(12) The value of k_m listed near the end of ref 10 resulted from an arithmetic error.

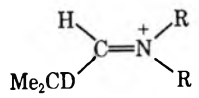
(13) J. Hine, B. C. Menon, J. Mulders, and J. P. Idoux, *J. Org. Chem.*, **32**, 3850 (1967).

(14) C. W. Davies, *J. Chem. Soc.*, 2093 (1938).

(15) J. N. Brønsted, *Z. Physik. Chem.*, **102**, 169 (1922); **115**, 337 (1925).

stants. The values of k_i and k'_iK_I obtained were within 3% of the values obtained neglecting such ionic strength effects, but k''_iK_{IH} was much smaller (0.040 M^{-1} sec^{-1}) and the standard deviation of the fit increased to 14%. We feel that this procedure, which requires the evaluation of the activity coefficients of a triply charged ion, is not very reliable and, largely because the k''_iK_{IH} value obtained is implausible, prefer the treatment in which ionic strength effects on rate constants were neglected. Nevertheless we feel that the value of k''_iK_{IH} obtained is much less reliable than the values of k'_iK_I and k_i. Other sets of restrictions on the nine constants in eq 11 led to implausible sets of rate constants with values of k'_iK_I, k''_iK_{IH}, and other constants that often differed considerably from the values obtained by the method described above, but the values of k_i were all constant within 15%.

A kinetic equation like eq 11 may be written for the dedeuteration of isobutyraldehyde-*2-d* in the presence of *N*,*N*′-dimethylethylenediamine, but the relative rate of exchange *via* iminium ions may be affected by the fact that the only iminium ions possible are of the type of ion **1**, formed from a secondary amine. In a study



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of catalysis of the dedeuteration of isobutyraldehyde-*2-d* by simple secondary amines, no evidence for reaction *via* iminium ions was obtained.[9] Least squares treatments with plausible restrictions gave sets of rate constants that corresponded to some exchange *via* iminium ions and permitted the calculation of the k_{obsd} values in Table III with standard deviations around 10%. However, when catalysis *via* iminium ion formation was completely neglected and only the restriction (based on a Brønsted β of 0.5) that $k_{dh} = 0.0259k_d$ was made, values for the two unknowns of 4.8×10^{-5} and 3.5×10^{-3} M^{-1} sec^{-1} were obtained for k_i and k_d, respectively. The k_{obsd} values may be calculated with a standard deviation of 11% from these rate constants, which were also used (with a pH of 8.66 and an aldehyde concentration of 0.053 M) in constructing the solid line in Figure 2. The value for log k_d falls about 0.2 log units below the line in the Brønsted plot for morpholine, piperazine, and piperidine, suggesting that the open-chain diamine is slightly more hindered than the cyclic amines. Brønsted plots of log k_i indicate that 1,3-dimethyl-2-isopropylimidazolidine is more hindered than *N*-methylmorpholine but no more hindered than a number of tertiary amines. Hindrance would be expected in view of the fact that the isopropyl group would have to be cis to at least one adjacent methyl group or cis to the unshared electron pair that is involved in removal of deuterium. In view of the plausible magnitude of the rate constants and the smallness in the improvement of the fit to the observed data obtained when catalysis *via* the formation of intermediate iminium ions is taken into account, we conclude that there may be some such catalysis, but it has not been established by our observations.

With *N*-methylethylenediamine we do not have equilibrium constants for reactions with isobutyraldehyde to form imidazolidines or imidazolidinium ions. Even if we did, the unsymmetrical nature of this base would make the detailed interpretation of kinetic data considerably more complicated than in the case of ethylenediamine or its *N*,*N*′-dimethyl derivative. Hence the dashed line in Figure 2 is simply a smooth curve that approximates the kinetic data.

Although a rate maximum and subsequent minimum is found with ethylenediamine and its *N*-methyl derivative, none appears with *N*,*N*′-dimethylethylenediamine. There are probably two major reasons for this. First, the equilibrium constant for the formation of an imidazolidine from isobutyraldehyde and *N*,*N*′-dimethylethylenediamine is only about one third as large as in the case of ethylenediamine itself. Second, 2-isopropylimidazolidine, which is 16 times as basic as its *N*,*N*′-dimethyl derivative and considerably less hindered, is a much better catalyst for the dedeuteration of isobutyraldehyde-*2-d*.

Experimental Section

The reagents used in this study have been described previously.[4,5] In some of the kinetic runs the pH of the reaction solution (which we take as $-\log a_{H^+}$, with activity coefficients being calculated from the Davies equation[14]) was not measured but was calculated from the concentrations of the various reagents that had been added and the relevant acidity constants and equilibrium constants for imidazolidine formation.[4] In some other kinetic runs the amount of hydrochloric acid or sodium hydroxide added was not carefully measured, but the pH was determined by use of a Radiometer pH meter (26c) and glass electrode (202b or 202c). In the remaining cases, in which the amount of added acid and the pH were both carefully measured, there were differences between the observed and calculated pH as large as 0.1. In the runs carried out using ethylenediamine and its *N*-methyl derivative, the reaction solutions were prepared from the free amine and the appropriate amount of standard hydrochloric acid. With *N*,*N*′-dimethylethylenediamine the dihydrochloride was used and the appropriate amount of standard sodium hydroxide was added.

In least squares treatments of the data it was the sum of the squares of the *fractional* deviations that was minimized.

Registry No.—Isobutyraldehyde-*2-d*, 4303-51-9; ethylenediamine, 107-15-3; *N*-methylethylenediamine, 109-81-9; *N*,*N*′-dimethylethylenediamine, 110-70-3.

1-(2-Imidazolin-2-yl)-2-imidazolines. I. The Structure of Jaffé's Base and the Chemistry of Related Compounds

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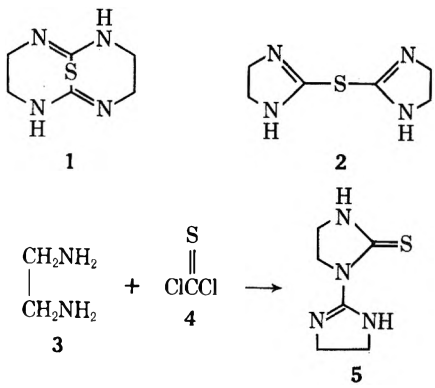
The synthesis of four potential starting materials for the preparation of 2-amino-1-(2-imidazolin-2-yl)-2-imidazolines is described. Treatment of 2-(methylthio)-2-imidazoline (**6**) with 2-(methylthio)-2-imidazoline hydriodide (**7**) gave 1-(2-imidazolin-2-yl)-2-(methylthio)-2-imidazoline hydriodide (**9**) and 1-(2-imidazolin-2-yl)-2-(methylthio)-2-imidazoline hydriodide methanethiol (**8**). Two minor products, 1-(2-imidazolin-2-yl)-2-[2-(methylthio)-2-imidazolin-1-yl]-2-imidazoline hydriodide (**10**) and 2,3,8,9-tetrahydro-5-(methylthio)-7*H*-imidazo[2,3-*b*][1,3,5]triazepine hydriodide (**11**), were also obtained. Reaction of 2-(methylthio)-2-imidazoline hydriodide (**7**) with triethylamine afforded triethyl[1-(2-imidazolin-2-yl)-2-imidazolin-2-yl]ammonium iodide hydriodide methanethiol (**12**) and 1-(2-imidazolin-2-yl)-2-(methylthio)-2-imidazoline dihydriodide methanethiol (**13**). The determination of the structures of the aforementioned compounds and their relationship to Jaffé's base, 1-(2-imidazolin-2-yl)-2-imidazolidinethione (**5**), is described. A novel hydrolysis, the transformation of 1-(2-imidazolin-2-yl)-2-(methylthio)-2-imidazoline dihydriodide methanethiol (**13**) to *S,S*-dimethyl dithiocarbonate (**17**) and 2-[(2-aminoethyl)amino]-2-imidazoline dihydroiodide (**18**), was observed. Evidence which suggests that previously described conversion of **6** to 1-(2-imidazolin-2-yl)-2-imidazolidinone (**14**)[4] proceeds *via* alkoxylimidazolinylimidazoline **21** is presented.

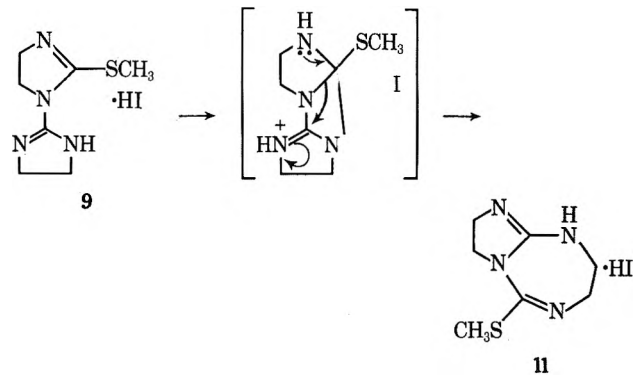
Structures **1**[1] and **2**[2] initially assigned to Jaffé's base, the product of the interaction of ethylenediamine (**3**) and thiophosgene (**4**),[1] were subsequently shown to be incorrect; the correct structure **5** was established



by the results of uv measurements[3] and confirmed by chemical interconversion.[4] During the course of an investigation concerned with the synthesis of 2-amino-1-(2-imidazolin-2-yl)-2-imidazolines as potential cardiovascular drugs, we obtained evidence compatible with structure **5** and studied some aspects of the chemistry of this class of compounds.

The starting material, 1-(2-imidazolin-2-yl)-2-(methylthio)-2-imidazoline hydriodide (**9**), required for the synthesis of 2-aminoimidazolinylimidazolines, was prepared by the reaction of 2-(methylthio)-2-imidazoline (**6**)[5] with 1 equiv of its hydriodide **7**.[6] Treatment of **6** with **7** gave **9** by precipitation from the reaction mixture and the corresponding methanethiol complex by concentration of the filtrate. Triimidazoline **10** and imidazotriazepine **11** were isolated by fractional crystallization of the residual reaction product.

The minor products were assigned triimidazoline and triazepine structures **10** and **11**, respectively, on the basis of plausible modes of formation, the former by reaction of either **8** or **9** with **6** and the latter by the internal rearrangement of **9** (and/or **8**) depicted below. The spectral properties (ir, uv, and nmr) of **10** and **11** were in accord with these structural postulations.

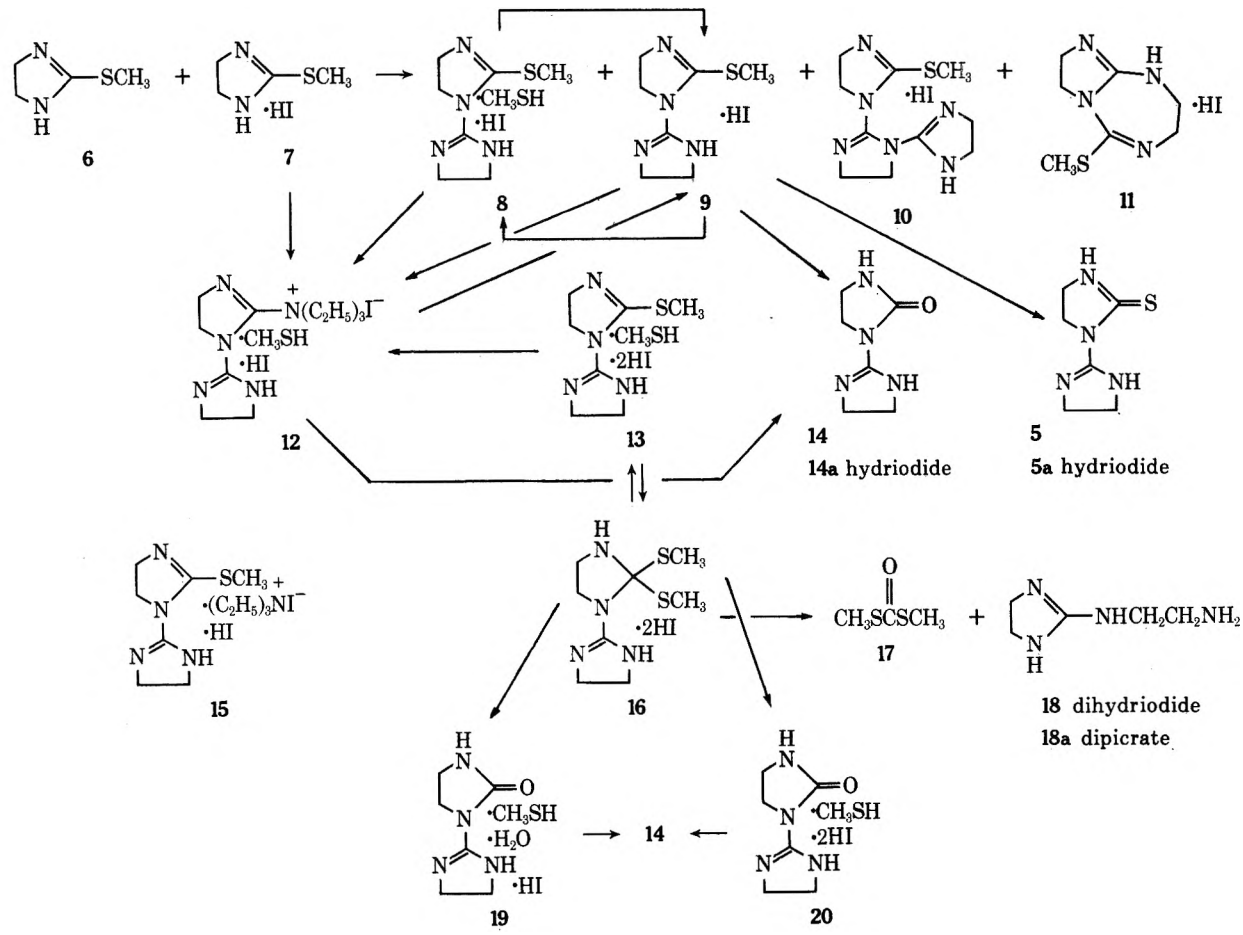


Two additional precursors of 2-aminoimidazolinylimidazolines became available when we found that reaction of imidazoline **7** with triethylamine afforded quaternary salt **12** by precipitation from the reaction mixture and methanethiol complex dihydriodide **13** by addition of 50% hydriodic acid to the filtrate.

Ammonolysis of **8** or **9** with triethylammonium iodide[7] and **13** with triethylamine gave quaternary iodide **12**. Hence, the imidazolinylimidazolines **8**, **9**, **12**, and **13** belong to the same chemical series and, as such, show ir absorption bands in the 1620–1660- and 1565–1600-cm^{-1} regions, characteristic of the imine and iminium functions,[8] respectively, and nmr signals in the 3.4–3.9-ppm region, assignable to the protons of the imidazoline rings.[9] As expected, the uv spectra of **8**, **9**, **12**, and **13** are transparent above 220 nm.

Structure **12** was assigned to the ammonolysis product solely on the basis of its solid-state (Nujol mull) ir spectrum, which exhibited an absorption band at 2550 cm^{-1}, a value within the accepted range for the sulfur–hydrogen stretching frequency of a thiol group.[10] That **12** exists in solution as the triethylammonium

(1) M. Jaffé and B. Kuhn, *Chem. Ber.*, **27**, 1663 (1894).
(2) T. B. Johnson and C. O. Edens, *J. Amer. Chem. Soc.*, **63**, 1058 (1941); T. B. Johnson and C. O. Edens, *ibid.*, **64**, 2706 (1942).
(3) H. Z. Lecher and K. Gubernator, *J. Amer. Chem. Soc.*, **75**, 1087 (1953); B. H. Chase and J. Walker, *J. Chem. Soc.*, 4443 (1955).
(4) G. I. Poos, J. Kleis, and C. K. Cain, *J. Org. Chem.*, **24**, 645 (1959).
(5) W. Wilson, *J. Chem. Soc.*, 1389 (1955).
(6) S. R. Aspinall and E. J. Bianco, *J. Amer. Chem. Soc.*, **73**, 602 (1951).
(7) S. B. Hendricks, *Z. Kristallogr.*, **67**, 42 (1928).
(8) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., Chapter 15.
(9) The Sadtler Standard Spectra, Sadtler Research Laboratories, Inc., Philadelphia, Pa., 1967, Nmr Spectra No. 3599.
(10) Reference 8, Chapter 22.



iodide complex **15** of **9** was indicated by nmr spectroscopy. Excluding the signals due to the ethyl groups, the spectra of **9** and **12** in deuteriodimethyl sulfoxide were strikingly similar, each displaying three-proton singlets at δ 2.5 ppm assignable to the methylthio groups,[11] in addition to those associated with the imidazoline moieties. Rapid deposition of **9** from a warm solution of **12** and dichloromethane provided supportive chemical evidence for this conclusion.

A comparison of the nmr spectra of **8** and **9** indicated that **8** was the methanethiol complex of **9**. Whereas the spectrum of **9** showed a three-proton singlet at δ 2.54 ppm, assignable to the methylthiol group,[11] that of **8** displayed two three-proton singlets in the same region (δ 2.40 and 2.60 ppm), one assignable to methanethiol and the other to the methylthio group. This indication was substantiated by the thermal demethylthiolation of **8** to **9** and by the methylthiolation of **9** to **8**.

Acid hydrolysis of imidazolinylimidazolines **9** and **12** afforded imidazolinylimidazolidinone **14** in fair yield. Numerous attempts to convert Jaffé's base **5** to **14** by exchange with mercuric oxide[4] and thereby interrelate this work with that previously described by others[1-4] failed to give **14**. Attempts to achieve the desired interrelation by methylation of **5** to **9** with methyl iodide also failed, hydriodide **5a** being the only identifiable product. The goal was finally achieved by the thermal demethylation of **9** to **5**. Thus, the structures of the reported imidazolinylimidazolines are established.

A novel hydrolysis of 2-methylthioimidazolinylimidazoline **13**, which established the presence of di(methylthiol)imidazolidine **16** in aqueous solution, was observed during the course of our initial attempts to correlate the gross structure of **13** with that of the cyclic urea **14**. Treatment of **13** with boiling hydriodic acid gave *S,S*-dimethyl dithiocarbonate (**17**) and 2-[(2-aminoethyl)amino]-2-imidazoline dihydriodide (**18**) in comparable yields. The hydrolysis products, carbonate **17**[12] and imidazoline dipicrate **18a**,[13] were identical with authentic samples prepared by previously described procedures. Hydrolysis under milder conditions afforded a low yield of the expected cyclic urea **20**. Neutralization of **20** furnished **14**.

Even though **13** is recrystallizable from methanol, prolonged dissolution in this solvent results in extensive decomposition to imidazolinone **19**. Neutralization of **19** gave **14**.

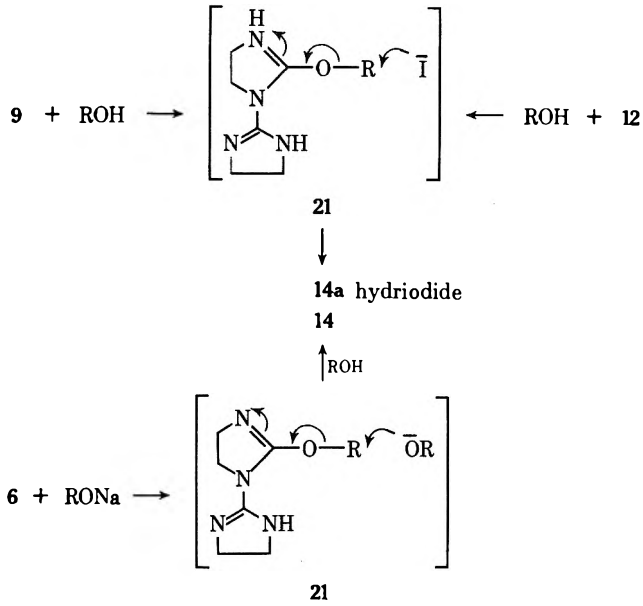
Methylthioimidazolinylimidazoline **9** and quaternary salt **12** reacted slowly with predried boiling methanol and 2-propanol under a blanket of nitrogen to give imidazolinylimidazolidinone **14a** in 25–30% yield in addition to unchanged **9** and **12** and were refractive in boiling 1-butanol, a weaker nucleophile than the primary and secondary alcohols. Hence, the conversion of **9** and **12** to **14a** was not a simple hydrolysis promoted by trace amounts of water but, more likely, involved alcoholysis of **9** and **12** to alkoxyimidazolinylimidazoline **21** followed by dealkylation of **21** by iodide to **14a**.

These observations coupled with the formation of **9** from **6** and **7** suggest that alkoxylimidazolinylimidazo-

(11) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Elmsford, N. Y., 1969, p 164.

(12) H. Pelster and E. Muehlbauer, German Patent 1,131,205 (1964); *Chem. Abstr.*, **62**, P6398*b* (1965).

(13) A. F. McKay, M. N. Buchanan, and G. A. Grant, *J. Amer. Chem. Soc.*, **71**, 766 (1949).



line 21 is an intermediate in the reported conversion[4] of 6 to 14 by ethanolic sodium ethoxide, the ethoxide acting as a base for the transformation of 6 to 21 and a nucleophile for the transformation of 21 to 14.

Methylthioimidazolinylimidazolines 8, 9, 12, and 13 react with a variety of amines to give 2-aminoimidazolinylimidazolines. These compounds show interesting biological activities, which will be the subject of forthcoming publications.[14,15]

Experimental Section[16]

Reaction of 2-(Methylthio)-2-imidazoline (6) with 2-(Methylthio)-2-imidazoline Hydriodide (7).—A solution of imidazoline 6 (116 g, 1.00 mol), imidazoline hydriodide 7 (244 g, 1.00 mol), and acetonitrile (distilled from calcium hydride) (700 ml) was heated under reflux for 1.5 hr while a *moderate* stream of nitrogen was passed through the reaction mixture. The solution was allowed to stand at room temperature for 48 hr. The precipitate was collected, yield 25 g (8.0%) of 1-(2-imidazolin-2-yl)-2-(methylthio)-2-imidazoline hydriodide (9), mp 176–178° (resolidified) and 230–250°.

An analytical sample, prepared by repeated recrystallization from 2-propanol, had mp 173–175° (resolidified) and 230–250° dec; uv max 218 nm (ε 14,600); ir 1620 (C=N$^+$), 1565 cm^{-1} (C=N); nmr δ 2.54 (s, 3, CH_3S), 3.71, 3.91 (s, 8, CH_2CH_2), and 8.70 (D_2O-exchangeable broad m, 2, NH_2).

Anal. Calcd for $C_7H_{13}IN_4S$: C, 26.93; H, 4.20; I, 40.65; N, 17.95. Found: C, 27.22; H, 4.16; I, 40.79; N, 17.84.

The filtrate was concentrated to a volume of 400 ml and the precipitate was collected. Fractional recrystallization from acetonitrile and 2-propanol gave 103 g (29%) of 1-(2-imidazolin-2-yl)-2-(methylthio)-2-imidazoline hydriodide methanethiol (8) mp 101–102°, which was recrystallized from acetonitrile: mp 103–104° dec; uv max 219 nm (ε 47,700); ir 1660 (C=N$^+$), 1585 cm^{-1} (C=N); nmr δ 2.40 (s, 3, CH_3S), 2.60 (s, 3, CH_3S), 3.33 (s, 1, SH), 3.44 (s, 4, CH_2CH_2), 3.67 (s, 4, CH_2CH_2), and 8.1 (D_2O-exchangeable broad m, NH, NH_2^+).

Anal. Calcd for $C_8H_{17}IN_4S_2$: C, 26.67; H, 4.76; I, 35.22; N, 15.55; S, 17.80. Found: C, 26.82; H, 4.82; I, 35.16; N, 15.61; S, 17.79.

Also obtained was 7.05 g (1.9%) of 1-(2-imidazolin-2-yl)-2-[2-(methylthio)-2-imidazolin-1-yl]-2-imidazoline hydriodide (10): mp 191–192° dec; uv max 217 nm (ε 40,800); ir 1712 (C=N$^+$), 1680, 1585 cm^{-1} (C=N); nmr δ 2.33 (s, 3, CH_3S), 3.8 (m, 12, CH_2CH_2) and 9.3 (D_2O-exchangeable broad s, 2, NH_2).

Anal. Calcd for $C_{10}H_{17}IN_6S$: C, 31.59; H, 4.51; I, 33.37; N, 22.10; S, 8.73. Found: C, 31.61; H, 4.51; I, 33.20; N, 22.14; S, 8.82.

Also obtained was 1.9 g (0.5%) of 2,3,8,9-tetrahydro-5-(methylthio)-7*H*-imidazo[2,3-*b*][1,3,5]triazepine hydriodide (11): mp 183–184°; uv max 219 nm (ε 26,500); ir 1685 (C=N$^+$), 1550 cm^{-1} (C=N); nmr δ 2.35 (s, 3, CH_3S) 3.1–4.4 (m, 9, CH_2CH_2, NH), and 8.8 (D_2O-exchangeable broad m, 1, $^+$NH).

Anal. Calcd for $C_7H_{13}IN_4S$: C, 26.93; H, 4.20; I, 40.65; N, 17.95. Found: C, 27.15; H, 4.22; I, 40.61; N, 17.92.

The base of 11 had mp 167–169°; uv max end absorption; ir 1670, 1610 cm^{-1} (C=N); nmr ($CDCl_3$) δ 2.25 (s, 3, CH_3S), 3.0–4.0 (m, 8, CH_2CH_2), and 6.25 (s, 1, NH).

Anal. Calcd for $C_7H_{12}N_4S$: C, 45.63; H, 6.56; N, 30.41; S, 17.40. Found: C, 46.03; H, 6.70; N, 30.27; S, 17.04.

Conversion of 1-(2-Imidazolin-2-yl)-2-(methylthio)-2-imidazoline Hydriodide (9) to 1-(2-Imidazolin-2-yl)-2-(methylthio)-2-imidazoline Hydriodide Methanethiol (8).—A solution of imidazoline 9 (3.0 g, 9.6 mmol), methylmercaptan (25 g, 0.52 mol), and acetonitrile (175 ml) was allowed to stand at 0° for 5 min and then evaporated. Trituration of the residue with acetone gave 2.28 g (76%) of unchanged imidazoline 9, mp 181–182° (resolidified) and 230–250°, alone and admixed with an authentic sample of 9, and 0.10 g (12%) of methanethiol complex 8, mp 100–102°, alone and admixed with an authentic sample of 8.

The ir spectra of 9 and 8, so obtained, were identical with those of the authentic samples.

Demethylthiolation of 1-(2-Imidazolin-2-yl)-2-(methylthio)-2-imidazoline Hydriodide Methanethiol (8).—A solution of methanethiol complex 8 and acetonitrile (100 ml) was heated under reflux for 66 hr while a vigorous stream of nitrogen was passed through the reaction mixture and then allowed to cool to room temperature. The precipitate was collected, washed with acetone, and dried, yield 1.05 g (66%) of imidazoline 9, mp 183–185° (resolidified) and 230–250° dec, alone or admixed with a reference sample.

The ir spectra of the two samples were identical.

Triethyl[1-(2-imidazolin-2-yl)-2-imidazolin-2-yl]ammonium Iodide Hydriodide Methanethiol (12) and 1-(2-Imidazolin-2-yl)-2-(methylthio)-2-imidazoline Dihydriodide Methanethiol (13).—A solution of 2-(methylthio)-2-imidazoline hydriodide (7) (244 g, 1.00 mol), triethylamine (101 g, 1.00 mol), and 2-propanol (freshly distilled from calcium hydride) (1 l.) was heated under reflux for 2 hr while a vigorous stream of N_2 was passed through the solution. The reaction mixture was allowed to cool to room temperature and the precipitate was collected. Recrystallization from 2-propanol gave 79.7 g (30%) of quaternary salt 12: mp 169–172° (resolidified) and 245–255° dec; uv max end absorption; ir 3300, 3150 (NH$^+$), 2550 (SH), 1630 (C=N$^+$), 1600 cm^{-1} (C=N); nmr δ 1.15 (t, 9, J = 6 Hz, CH_3), 2.51 (s, 3, CH_3S), 3.13 (q, 6, J = 6 Hz, CH_2), 3.70 and 3.86 (s, 8, CH_2CH_2), and 8.6 (D_2O-exchangeable broad m, 3 H, NH$^+$, SH).

Anal. Calcd for $C_{13}H_{29}I_2N_5S$: C, 28.85; H, 5.40; I, 46.89; N, 12.94; S, 5.92. Found: C, 28.98; H, 5.42; I, 46.75; N, 12.79; S, 5.94.

Hydriodic acid (50%) (140 ml) was added to the above filtrate and, after 30 min, the solid was collected and recrystallized from 2-propanol–water (4:1); yield 59.6 g (12%) of methanethiol dihydriodide 13: mp 162–164°; uv max 218 nm (ε 36,800); ir 1668 (C=N$^+$), 1600, 1545 cm^{-1} (C=N); nmr (D_2O) δ 2.84, 2.89 (s, 6, CH_3S), and 3.9 (m, 8, CH_2CH_2).

Anal. Calcd for $C_8H_{18}I_2N_4S_2$: C, 19.68; H, 3.72; I, 52.00; N, 11.48; S, 13.13. Found: C, 19.97; H, 3.80; I, 52.13; N, 11.26; S, 13.22.

Preparation of 1-(2-Imidazolin-2-yl)-2-(methylthio)-2-imidazoline Dihydriodide Methanethiol (13) from 2-(Methylthio)-2-imidazoline (6) and 2-(Methylthio)-2-imidazoline Hydriodide (7).—A solution of imidazoline 6 (58.0 g, 0.500 mol), hydriodide 7 (122 g, 0.500 mol), and acetonitrile (1.5 l.) was heated under reflux for 2 hr and then allowed to cool to room temperature. Hydriodic acid (50%, 65 ml) was added and the precipitate was

(14) R. R. Wittekind, T. Capiris, J. Fahey, and J. Shavel, Jr., to be submitted for publication in *J. Med. Chem.*

(15) R. R. Wittekind, H. Kaplan, T. Capiris, J. Fahey, and J. Shavel, Jr., to be submitted for publication in *J. Pharm. Sci.*

(16) Melting points were determined in open capillary tubes on a Thomas-Hoover Unimelt, previously calibrated against known standards. The uv spectra were determined in 95% ethanol with a Beckman DK-1 spectrophotometer. The ir spectra were determined in Nujol mulls, unless otherwise indicated, on a Baird 455 spectrophotometer. The nmr spectra were measured in deuteriodimethyl sulfoxide, unless otherwise indicated, on a Varian A-60 spectrometer with tetramethylsilane as the internal standard. The mass spectra of all new compounds were determined on a Consolidated Electronics Corp. Model 21-103C or an Associated Electronic Industries MS 902 spectrograph and showed the expected molecular ion.

collected. Recrystallization from methanol gave 75.0 g (30%) of dihydriodide **13**, mp 160–161°, alone and admixed with a sample described in the preceding section.

Conversion of 1-(2-Imidazolin-2-yl)-2-(methylthio)-2-imidazoline Hydriodide (9) to Triethyl[1-(2-imidazolin-2-yl)-2-imidazolin-2-yl]ammonium Iodide Hydriodide Methanethiol (12).—A solution of imidazoline **9** (1.06 g, 3.39 mmol), triethylammonium iodide (0.777 g, 3.39 mmol), and 2-propanol (40 ml) was heated under reflux for 1 hr while a stream of N_2 was passed through the reaction mixture. The solution was allowed to cool to room temperature and the solid was collected; yield 1.29 g (77%) of quaternary salt **12**, mp 169–172° (resolidified) and 240–250° dec, alone or admixed with the initial sample.

The ir spectra of the two samples were identical.

Conversion of 1-(2-Imidazolin-2-yl)-2-(methylthio)-2-imidazoline Hydriodide Methanethiol (8) to Triethyl[1-(2-imidazolin-2-yl)-2-imidazolin-2-yl]ammonium Iodide Hydriodide Methanethiol (12).—A solution of imidazoline **8** (5.4 g, 0.015 mol), triethylammonium iodide (3.4 g, 0.015 mol), and 2-propanol (20 ml) was heated under reflux for 23 hr and allowed to cool to room temperature. The solid was collected. Recrystallization from 2-propanol gave 3.0 g (37%) of quaternary salt **12**, mp 169–171° (resolidified) and 245–250° dec, alone or admixed with an authentic sample of **12**.

The ir spectra of the two samples were superimposable.

Conversion of 1-(2-Imidazolin-2-yl)-2-(methylthio)-2-imidazoline Dihydriodide Methanethiol (13) to Triethyl[1-(2-imidazolin-2-yl)-2-imidazolin-2-yl]ammonium Iodide Hydriodide Methanethiol (12).—A solution of imidazoline **13** (4.88 g, 0.0100 mol), triethylamine (1.05 g, 0.0102 mol), and 2-propanol (110 ml) was boiled under reflux for 35 min, during which time a steady stream of nitrogen was bubbled through the solution. The reaction mixture was allowed to cool to room temperature and the precipitate was collected. Recrystallization from 2-propanol gave 2.72 g (50%) of quaternary salt **12**, mp 169–172° (resolidified) and 241–250° dec, alone or admixed with an authentic sample from the initial experiments.

The ir spectra of the samples were identical.

Conversion of Triethyl[1-(2-imidazolin-2-yl)-2-imidazolin-2-yl]ammonium Iodide Hydriodide Methanethiol (12) to 1-(2-imidazolin-2-yl)-2-(methylthio)-2-imidazoline Hydriodide (9).—A mixture of quaternary salt **12** (8.43 g, 0.0155 mol) and dichloromethane (300 ml) was heated for 45 min and allowed to cool to room temperature. Unchanged quaternary salt **12** (2.92 g, 0.00538 mol) was collected. The filtrate was allowed to stand for several hours. The solid was collected; yield 3.00 g (11%) of **9**, mp 176–178° (resolidified) and 230–250°, alone and admixed with a sample prepared by the method described in the preceding experiment.

Hydrolysis of 1-(2-Imidazolin-2-yl)-2-(methylthio)-2-imidazoline Hydriodide (9).—A solution of imidazoline **9** (5.40 g, 0.0173 mol), water (100 ml), and 50% hydriodic acid (0.75 ml) was heated under reflux for 1 hr and then evaporated under reduced pressure. Trituration of the residue with 2-propanol followed by recrystallization from 2-propanol gave 3.57 g (73%) of 1-(2-imidazolin-2-yl)-2-imidazolidinone hydriodide (**14a**): mp 256–258° dec; uv max end absorption; ir 1740 (C=O), 1650 cm^{-1} (C=N^+); nmr δ 3.5 (m, 9, CH_2CH_2, NH) and 8.2 (D_2O-exchangeable broad m, 2, NH^+).

Anal. Calcd for $C_6H_{11}IN_4O$: C, 25.55; H, 3.93; I, 44.99; N, 19.86; O, 5.67. Found: C, 25.64; H, 4.15; I, 44.72; N, 19.65; O, 5.91.

Hydrolysis of Triethyl[1-(2-imidazolin-2-yl)-2-imidazolin-2-yl]ammonium Iodide Hydriodide Methanethiol (12).—A solution of quaternary salt **12** (42.8 g, 0.0870 mol), water (150 ml), and 50% hydriodic acid (1.5 ml) was heated under reflux for 7 days and then the solution was evaporated to dryness under reduced pressure. Recrystallization of the residue from 2-propanol gave 5.01 g (21%) of imidazolidinone hydriodide **14a**, mp 256–258° dec, alone or admixed with the sample obtained from the preceding experiment.

The ir spectra of the two samples were also identical.

The free base of **14a** was obtained by the usual procedure (neutralization with 1 *N* NaOH solution and extraction with Et_2O) and had mp 198–199° dec (lit.[4] mp 200–204°); uv max end absorption; ir 3380, 3200 (NH), 1720 (C=O), 1610 cm^{-1} (C=N); nmr δ 3.5 (m, 8, CH_2CH_2) and 7.3 (D_2O-exchangeable v br m, 2, NH).

Anal. Calcd for $C_6H_{10}N_4O$: C, 46.74; H, 6.54; N, 36.34. Found: C, 47.01; H, 6.74; N, 36.38.

Demethylation of 1-(2-Imidazolin-2-yl)-2-(methylthio)-2-imidazoline Hydriodide (9).—A solution of methylthioimidazoline hydriodide **9** (12.5 g, 0.0400 mol) and acetonitrile (300 ml) was heated under reflux under an atmosphere of nitrogen for 1 week and then cooled in an ice bath. The solid was collected. Recrystallization from 95% ethanol–water (5:1) gave 3.35 g (28%) of 1-(2-imidazolin-2-yl)-2-imidazolidinethione hydriodide (**5a**): mp 282–284° dec (lit.[4] mp 296–299° dec); uv max 223 nm (ϵ 26,700), 265 (12,600); ir 1630 (C=N^+), 1590 (C=N), 1120 cm^{-1} (C=S); nmr δ 4.0 (m, 9, CH_2CH_2, NH) and 9.7 (D_2O-exchangeable v br m, 2 H, NH^+).

Anal. Calcd for $C_6H_{11}IN_4S$: C, 24.17; H, 3.72; I, 42.56; N, 18.79; S, 10.75. Found: C, 24.32; H, 3.77; I, 42.75; N, 18.83; S, 10.59.

Methanolysis of 1-(2-Imidazolin-2-yl)-2-(methylthio)-2-imidazoline Dihydriodide Methanethiol (13).—Imidazoline **13** (60.0 g, 0.123 mol) was dissolved in the minimum volume of boiling methanol and the solution was allowed to stand at room temperature for 3 days. The precipitate was collected. Recrystallization from ethanol gave 20.1 g (47%) of 1-(2-imidazolin-2-yl)-2-imidazolidinone hydriodide methanethiol hydrate (**19**): mp 160–161° dec; uv max 216 nm (ϵ 18,700); ir 1670 (C=O), 1640 cm^{-1} (C=N^+); nmr δ 2.23 (s, 3, CH_3S), 3.25 (m, 6 H, CH_2CH_2, H_2O), 3.62 (s, 4, CH_2CH_2), and 7.9 (D_2O-exchangeable broad m, 4, NH).

Anal. Calcd for $C_7H_{17}IN_4O_2S$: C, 25.54; H, 4.29; I, 38.54; N, 17.02; O, 4.88; S, 9.74. Found: C, 25.75; H, 4.63; I, 38.15; N, 17.67; O, 5.14; S, 10.48.

Neutralization of 1-(2-Imidazolin-2-yl)-2-imidazolidinone Hydriodide Methanethiol Hydrate (19).—Dissolution of hydriodide **19** in 1 *N* NaOH solution followed by extraction and recrystallization from benzene gave imidazolidinone **14**, mp 200–203° dec (lit.[4] mp 200–205°) alone or admixed with the sample derived from **9**.

The ir spectra of the samples were identical.

Hydrolysis of 1-(2-Imidazolin-2-yl)-2-(methylthio)-2-imidazoline Dihydriodide Methanethiol (13).—A solution of imidazoline **13** (218 g, 0.486 mol), water (1.2 l.), and 50% HI solution (25 ml) was heated under reflux for 1 hr and then evaporated to dryness under reduced pressure. Recrystallization of the residue from 2-propanol–water (9:1) gave 14.9 g (6.7%) of 1-(2-imidazolin-2-yl)-2-imidazolidinone dihydriodide methanethiol (**20**): mp 258–259° dec; uv max 218 nm (ϵ 37,800); ir 1690 (C=O), 1550 cm^{-1} (C=N^+); nmr δ 2.44 (m, 4, CH_3SH), 2.8–4.2 (m, 8, CH_2CH_2), and 8.5 (D_2O-exchangeable v br m, 4, NH^+).

Anal. Calcd for $C_7H_{16}I_2N_4OS$: C, 18.35; H, 3.52; N, 12.23; O, 3.49. Found: C, 18.60; H, 3.60; N, 12.02; O, 3.70.

Neutralization of **20** with 5% NaOH solution followed by extraction with CH_2Cl_2 gave 37% of the base **14**, mp 199–200° dec alone or admixed with an authentic sample, prepared as previously described.

The ir spectra of the samples were identical.

A solution of imidazolidine **13** (244 g, 0.500 mol), water (1.2 l.), and 50% hydriodic acid (10 ml) was boiled under reflux for 1 hr and allowed to cool to room temperature. The layers were separated and the aqueous phase was extracted (CH_2Cl_2). The organic extracts were dried (Na_2SO_4) and evaporated. Distillation of the residual oil gave 20 g (33%) of *S,S*-dimethyl dithiocarbonate (**17**): bp 61–62° (17 mm); uv max 215 nm (ϵ 2500), 248 (4450); ir (CH_2Cl_2) 1640 cm^{-1} (C=O); nmr (CCl_4) δ 2.37 (s, 6,[17] CH_3S).

Anal. Calcd for $C_3H_6OS_2$: C, 29.49; H, 4.95; O, 13.10; S, 52.48. Found: C, 29.58; H, 4.94; O, 13.43; S, 52.21.

The filtrate was evaporated. 2-Propanol was added to the residue and the solid was collected. Recrystallization from 2-propanol–water (15:1) gave 60.7 g (31%) of 2-[(2-aminoethyl)amino]-2-imidazoline dihydriodide (**18**): mp 210–212°; uv max 218 nm (ϵ 31,500); ir 1655 cm^{-1} (C=N^+); nmr δ 2.6–3.5 (m, 4, CH_2CH_2), 3.66 (s, 4, CH_2CH_2), and 8.1 (D_2O-exchangeable broad m, 4, NH).

Anal. Calcd for $C_5H_{14}I_2N_4$: C, 15.64; H, 3.67; N, 14.59; I, 66.10. Found: C, 15.93; H, 3.69; N, 14.71; I, 66.29.

2-[(2-Aminoethyl)amino]-2-imidazoline dipicrate, mp 198–200° (lit.[13] mp 199–200°), was prepared by basification (NaOH)

(17) Relative to benzene as the internal standard.

of an aqueous solution of the corresponding dihydriodide, evaporation, dissolution of the residue in ethanol, and treatment with picric acid and showed an ir spectrum identical with that of an authentic sample.[13]

Alcoholysis of 1-(2-Imidazolin-2-yl)-2-(methylthio)-2-imidazoline Hydriodide (9) and Triethyl[1-(2-imidazolin-2-yl)-2-imidazolin-2-yl]ammonium Iodide Hydriodide Methanethiol (12).

A. With Methanol and 2-Propanol.—A solution of 9 or 12 (0.020 mol) and the alcohol (distilled from calcium hydride, 25 ml) was heated under reflux for 5 days while a stream of nitrogen was bubbled through the reaction mixture and then allowed to cool to room temperature. The precipitate was collected; yield 0.005–0.0067 mol (25–30%) of imidazolidinone hydriodide **14a**, mp 255–257° dec alone or admixed with an authentic sample.

The ir spectra of the samples were identical.

B. With *tert*-Butyl Alcohol.—A solution of 9 or 12 (0.020 mol) and *tert*-butyl alcohol (distilled from calcium hydride, 175 ml) was treated as above to give 0.0180–0.0185 mol (90–93%) of unchanged 9 or 12 by mixture melting point determination and ir spectroscopy.

Registry No.—**5a**, 38631-03-7; **6**, 20112-79-2; **7**, 5464-11-9; **8**, 38621-46-4; **9**, 36858-50-1; **10**, 38631-06-0; **11**, 38631-07-1; **11** HI, 38631-08-2; **12**, 36813-47-5; **13**, 38621-48-6; **14a**, 38631-09-3; **14a** HI, 38677-78-0; **17**, 868-84-8; **18**, 38631-10-6; **19**, 38744-27-3; **20**, 38621-49-7.

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5-Imino-2-oxo-1,2,3-oxathiazolidines[1]

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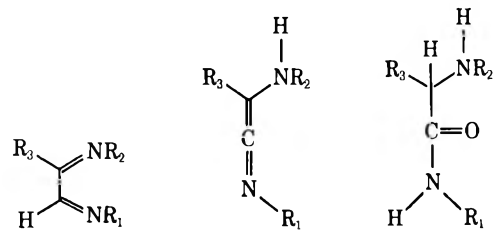
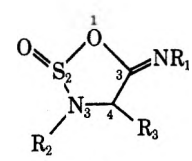
A series of aryl and aliphatic substituted 2-aminoamides have been prepared and treated with thionyl chloride and base to give 5-imino-2-oxo-1,2,3-oxathiazolidines in good yield. This structure was assigned on the basis of analytical, chemical, and spectral data as well as by comparisons with other 2-oxo-1,2,3-oxathiazolidines obtained previously. Asymmetry at sulfur is noted.

As part of our continuing study on the reactions of isonitriles with imines,[3] it became necessary to develop a general synthesis for unsymmetrically N-substituted 1,4-diaza-1,3-butadienes (**1**). Since a direct synthesis of **1** from 1,2-dicarbonyl compounds was precluded by imine interchange reactions,[4] we sought alternative approaches to **1**. Dehydration of readily available 2-aminoamides (**3**) to 2-aminoketenes (**2**) which might



1 **2** **3**

in turn be isomerizable to **1** constituted one attractive path.[5] Initial attempts at dehydration with PCl_5 and subsequent base treatment[7] or with P_2O_5[8] failed to give recognizable products. Reaction of **3** with thionyl chloride and subsequent treatment of the product with pyridine yielded compounds to which we have assigned the 5-imino-2-oxo-1,2,3-oxathiazolidine structure (**4**). In this paper, we wish to discuss the synthesis and structural assignment of this novel *functionally substituted* example of a relatively unexplored heterocyclic system.[9-13]



4

4	R_1	R_2	R_3
a	*o*-$C_6H_4CH_3$	*t*-Bu	H
b	*o*-$C_6H_4CH_3$	C_6H_5	H
c	*t*-Bu	C_6H_5	H
d	*i*-Pr	*t*-Bu	H
e	$CH_2C_6H_4$	*t*-Bu	H
f-1	C_6H_5	*t*-Bu	C_6H_5
f-2	C_6H_5	*t*-Bu	C_6H_5

Results and Discussion

A series of 2-aminoacetamides was prepared from the reactions of the appropriate 2-chloroacetamides and excess primary amines in benzene. These 2-aminoacetamides were in turn treated with excess thionyl chloride and subsequently (after removal of unreacted thionyl chloride) with excess pyridine. Equivalent results were obtained when base (triethylamine) was present during the thionyl chloride reaction.

The product in each reaction (Table I) was neutral and gave a mass spectral parent ion which corresponded to the original molecule plus SO minus 2 H. This empirical formula was confirmed by elemental analysis. The ir spectra indicated that the amide C=O band had

(1) Support of this work by the National Science Foundation (Grant GP-17642) is gratefully acknowledged.

(2) National Science Foundation Undergraduate Research Fellow, summer 1971.

(3) J. A. Deyrup, M. M. Vestling, W. V. Hagan, and H. J. Yun, *Tetrahedron*, **25**, 1467 (1969).

(4) *Cf.* S. Dayagi and Y. Degani in "The Chemistry of the Carbon–Nitrogen Double Bond," S. Patai, Ed., Interscience, New York, N. Y., 1970, p 81.

(5) One previous publication reported the synthesis of an α-acyl-α-aminoketene. No mention was made of its tautomerization.[6]

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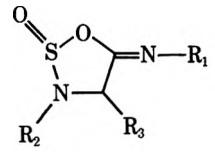
(13) F. Wudl and T. B. K. Lee, Abstracts, 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 1971, No. ORGN 177.

TABLE I

5-IMINO-2-OXO-1,2,3-OXATHIAZOLIDINES[a]

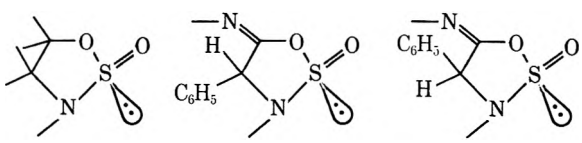


Compd	R_3	R_1	R_2	Yield, %	Mp, °C	Ir C=N, μ	Nmr data δ ppm[b] R_3[c]	H (JAB in Hz, ΔAB in Hz)	R_1 (JAB in Hz, ΔAB in Hz)	R_2
4a	H	o-$C_6H_4CH_3$	t-Bu	76	123–125[d]	5.81	4.09	(15.9, 19.2)	7.23 (s), 2.27 (s)	1.40 (s)
4b	H	o-$C_6H_4CH_3$	C_6H_5	56	129–131[e]	5.83	4.49	(15.7, 12.8)	6.90–7.60 (m), 2.30 (s)	6.90–7.60 (m)
4c	H	t-Bu	C_6H_5	41	84–86[d]	5.81	4.30	(15.5, 15.2)	1.65 (s)	6.90–7.54 (m)
4d	H	i-Pr	t-Bu	48	73–75[d]	5.83	3.93	(16.0, 22.0)	1.11–1.50 (m)	1.37 (s)
4e	H	CH_2–C_6H_5	t-Bu	64	88–89[d]	5.85	3.98	(16.0, 15.2)	4.70 (15.3, 36.7), 7.29 (s)	1.35 (s)
4f-1	C_6H_5	C_6H_5	t-Bu	80[f]	152–153.5[e]	5.87	7.20–7.90 (m), 5.11 (s)		7.20–7.90 (m)	1.36 (s)
4f-2	C_6H_5	C_6H_5	t-Bu		145–147[e]	5.81	7.25–7.55 (m), 5.25 (s)		7.25–7.55 (m)	1.30 (s)

[a] Satisfactory analytical values (±0.4% for C, H, N) for all compounds were reported: Ed. [b] Relative to tetramethylsilane (TMS) in deuteriochloroform. [c] When R_3 = H the values are for the center of the AB quartet. [d] From petroleum ether (bp 65–110°). [e] From absolute EtOH. [f] 4f-1 and 4f-2 were obtained in a 1:2 ratio.

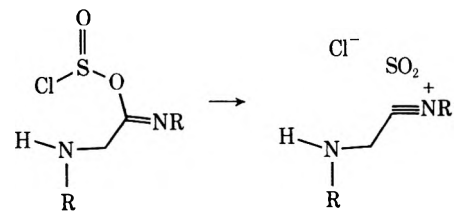
been replaced by an absorption at approximately 5.83 μ (Table I). This is consistent with the exocyclic imino ether substructure in **4**.[14] Other tautomeric structures were excluded by the absence of N–H or OH peaks. Additional support for structure **4** was provided by the mild, high yield (91%) acid hydrolysis of 3-*tert*-butyl-2-oxo-5-(*o*-toluidino)-1,2,3-oxathiazolidine (**4a**) to its precursor, 2-aminoacetamide (**3a**).

Further structural information was revealed by the nmr spectra of these compounds (Table I). The geminal methylene protons of compounds **4a–e** are in a nonequivalent environment as evidenced by their appearance as a doublet of doublets. The benzylic methylene group of compound **4e** also experiences an asymmetric situation. In the case of **4f**, a pair of isomers (**4f-1** and **4f-2**) could be separated by fractional recrystallization. These results require that **4** has a noncarbon dissymmetric center. Asymmetry at sulfur and long-range anisotropic effects by the S–O bond have been discussed previously for the parent 2-oxo-1,2,3-oxathiazolidines (**5**).[12] Thus **4f-1** and **4f-2** must differ with respect to the cis–trans relationship between the sulfur–oxygen bond and the phenyl group (**6**).[15]



5 **6**

Reasons for the formation of the 5-imino-2-oxo-1,2,3-oxathiazolidines and failure to observe the desired imidoyl chlorides are not totally clear. If initial reaction occurs at oxygen to give **7**, then neighboring-group participation by nitrogen must be faster than ionization to nitrilium salt **8**. Protonation on the amino nitrogen (when base is not present during the thionyl chloride reaction) apparently inhibits ionization with loss of SO_2. Alternatively, thionyl chloride might initially react at the α nitrogen. Subsequent neighboring-group participation by the amide oxygen could then yield the product **4**. At the present time, we have no basis for choosing between these alternatives.



7 **8**

A wide variety of similarly functionalized heterocyclic systems should be available by application of the principle embodied in the formation of **4**. It is also worthy of note that formation of these 5-imino-2-oxo-1,2,3-oxathiazolidines results in the simultaneous protection of the nitrogen and activation of the amide. Synthetic utilization of this situation as well as further chemical study of this and related heterocycles is in progress.

Experimental Section

Melting points and boiling points are uncorrected. Ir spectra were recorded on a Perkin-Elmer 137 spectrophotometer. All nmr spectra were recorded on a Varian A-60A spectrometer. Mass spectra were obtained on a RMU 6E mass spectrometer. Microanalyses were obtained from Atlantic Microlab, Atlanta, Ga. 30308.

Chloroacetamides.—*N*-Benzyl-2-chloroacetamide,[16] 2-chloro-*o*-acetotoluidide,[17] *N*-*tert*-butyl-2-chloroacetamide,[18] *N*-isopropyl-2-chloroacetamide,[18] and 2-chlorophenylacetanilide[19] were prepared according to published procedures.[20]

General Procedure for Preparation of 2-Aminoacetamides.—Into a 250-ml round-bottomed flask equipped with a magnetic stirrer, heating mantle, and a reflux condenser was placed the 2-chloroacetamide (0.05 mol) in 100 ml of benzene along with the primary amine (0.5 mol). The reaction was refluxed for 14–60 hr under a nitrogen atmosphere. After this time the 2-amino-

(14) *Cf.* J. A. Deyrup and K. K. Killion, *J. Heterocycl. Chem.*, **9**, 1045 (1972).

(15) Uncertainties in ring and substituent conformation as well as in a precise knowledge of the S–O anisotropic effect precluded assignment of the cis–trans stereochemistry.

(16) E. K. Harvill, R. M. Herbst, and E. G. Schreiner, *J. Org. Chem.*, **17**, 1597 (1952).

(17) E. Abderhalden, E. von Ehrenwell, S. Schwab, and O. Yumstein, *Fermentforschung*, **13**, 408 (1932).

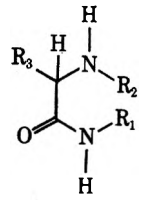
(18) A. J. Speziale and P. C. Hamm, *J. Amer. Chem. Soc.*, **78**, 2556 (1956).

(19) J. M. Sandri and E. K. Fields, U. S. Patent 3,280,032 (1966); *Chem. Abstr.*, **66**, 4733u (1967).

(20) *Cf.* reference 16.

TABLE II

2-AMINOACETAMIDES



Compd	R_3	R_2	R_1	Time, hr	Yield, %	Mp, °C, or bp (mm)	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
3a	H	*t*-Bu	*o*-$C_6H_4CH_3$	22	95	77–79[a]	70.87	9.15	12.72	70.76	9.26	12.71
3b	H	C_6H_5	*o*-$C_6H_4CH_3$	22	89	159.5–161[b]	74.97	6.71	11.66	74.82	6.77	11.55
3c	H	C_6H_5	*t*-Bu	14	51	72–74[c]	69.87	8.80	13.58	69.77	8.89	13.62
3d	H	*t*-Bu	*i*-Pr	21	86	72 (0.23)	62.75	11.70	16.26	62.65	11.66	16.15
3e	H	*t*-Bu	$CH_2C_6H_5$	21	96	36.5–37.5[a]	70.87	9.15	12.72	70.79	9.20	12.76
3f	C_6H_5	*t*-Bu	C_6H_5	60	58	123.5–125.5[d]	76.56	7.85	9.92	76.61	7.87	9.85

[a] From petroleum ether (bp 65–110°). [b] From absolute EtOH. [c] From C_6H_6 and petroleum ether (bp 65–110°). [d] From MeOH.

acetamide was extracted into 10% hydrochloric acid to separate it from neutral or acidic by-products and then the acid layer was made basic with 10% sodium hydroxide solution and extracted with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, filtered, and evaporated. The reactions and reaction products are summarized in Table II.

General Procedure for Preparation of 5-Imino-2-oxo-1,2,3-oxathiazolidines.—Into a 200-ml round-bottomed flask equipped with a heating mantle, a magnetic stirrer, a reflux condenser, and a drying tube was placed the 2-aminoacetamide (0.01 mol) in 100 ml of benzene with thionyl chloride (33.1 g, 20 ml, 0.278 mol). The solution was refluxed for 2 hr, cooled, and evaporated to ~10–15 ml to remove excess thionyl chloride. To the residue was added 100 ml of benzene and to this with stirring 25 ml of dry pyridine was slowly added. The resulting mixture was then extracted with 50 ml of water, 100 ml of 10% hydrochloric acid, 50 ml of 10% sodium hydroxide, and then 50 ml of water. The organic layer was dried with anhydrous magnesium sulfate, filtered, and evaporated to an oil. The resulting oil was crystallized from an appropriate solvent (see Table I).

The isomers of compound **4f** were separated by fractional crystallization since column chromatography over 5% deactivated alumina failed to produce separation. It was found that some isomer **4f-1** could be removed very efficiently from isomer **4f-2** by recrystallization from methanol.

As an example of an alternative procedure, a solution of thionyl chloride (0.72 ml, 0.01 mol) in 25 ml of benzene was added to a solution of 2-*tert*-butylamino-*o*-acetotoluidide (2.20 g, 0.01 mol) and triethylamine (2.79 ml, 0.02 mol) in 100 ml of benzene over 1 hr at room temperature. The solution was then refluxed for 2 hr. After the solution had cooled, the triethylamine hydrochloride precipitate was collected by filtration and washed with 50 ml of benzene. The combined filtrates were then washed with 100 ml of 10% HCl, 50 ml of 10% NaOH, and 50 ml of water. The organic layer was dried over anhydrous magnesium sulfate, filtered, and evaporated to a solid. The resulting solid was recrystallized once from absolute EtOH to give 1.93 g (73%) of a colorless crystalline solid, mp 123–125° (**4a**).

Acid Hydrolysis of 4a.—A solution of 666 mg (2.5 mmol) of **4a**, 20 ml of tetrahydrofuran, 10 ml of water, and 6 ml of concentrated hydrochloric acid was allowed to stand at room temperature for 24 hr. The tetrahydrofuran was then evaporated, and, after basification with 10% NaOH, the basic aqueous phase was extracted with chloroform. The dried chloroform extracts ($MgSO_4$) were evaporated to give a yellow solid. This solid was recrystallized from petroleum ether (bp 65–110°) to give 502 mg (91%) of a colorless crystalline solid which was identified as 2-*tert*-butylamino-*o*-acetotoluidide (**3a**) by comparing melting point and ir and nmr spectra with those of an authentic sample.

Registry No.—**3a**, 38630-92-1; **3b**, 38630-93-2; **3c**, 38630-94-3; **3d**, 38630-95-4; **3e**, 38630-96-5; **3f**, 38630-97-6; **4a**, 38630-98-7; **4b**, 38630-99-8; **4c**, 38631-00-4; **4d**, 38631-01-5; **4e**, 38631-02-6; **4f-1**, 38630-66-9; **4f-2**, 38630-67-0.

Studies on Heterocage Compounds. IV.[1] The Through-σ-Bond Interaction of β-Amino Ketone Moiety in 1,3-Diazaadamantan-6-one and 3,6-Diazahomoadamantan-9-one Systems. Structure and Reactivity

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Some characteristic structural features of 5,7-diphenyl- (1a) and 5,7-dicarbomethoxy-1,3-diazaadamantan-6-one (1b) and 1,8-diphenyl- (2a) and 1,8-dicarbomethoxy-3,6-diazahomoadamantan-9-one (2b) are discussed in terms of uv, nmr, and ir spectral data, and pK_a' values. The β-amino ketone moiety in these compounds was shown to behave as an amide analog because of the through-σ-bond interaction of the lone electron pair on the nitrogen atom with the carbonyl π orbitals. Reaction of 1a with tosylhydrazide afforded no trace of the corresponding hydrazone but only 6-alcohol 8. Reaction of 1a with excess hydrazine hydrate in refluxing diethylene glycol gave hydrazone 7, which, on treatment with potassium *tert*-butoxide in dimethyl sulfoxide, gave also 8.

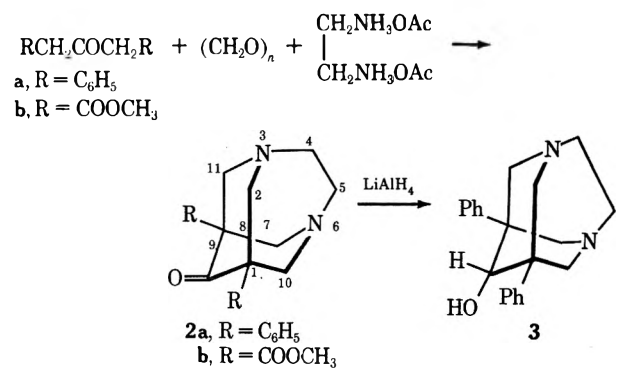
Although the through-σ-bond interaction of the appropriately oriented β-amino ketone moiety is well recognized by recent theoretical and spectroscopic (uv and CD) studies,[2-4] structure–reactivity correlations of such systems have not been extensively studied.[5] In a continuation of our recent studies on heterocage compounds,[6] this paper deals with some characteristic structural features and reactions of 1,3-diazaadamantan-6-one and 3,6-diazahomoadamantan-9-one systems, in which both the lone electron pair on nitrogen and the π orbitals of the C=O group can interact with the same C–C σ bond.

Results and Discussion

Synthesis.—5,7-Diphenyl- (**1a**) and 5,7-dicarbomethoxy-1,3-diazaadamantan-6-one (**1b**) were prepared by the Mannich condensation of dibenzyl ketone and dimethyl acetonedicarboxylate with formaldehyde and ammonia according to reported procedures.[7] By using ethylenediamine instead of ammonia in the above Mannich reactions, 1,8-diphenyl- (**2a**) and 1,8-dicarbomethoxy-3,6-diazahomoadamantan-9-one (**2b**) were obtained in 8 and 6% yields, respectively (Scheme I). Although the yields are very low, this reaction provides a facile one-step synthesis of the homoadamantane skeleton.[8]

Compound **2a** had a formula $C_{21}H_{22}N_2O$ from analysis and a mass spectral molecular ion peak at *m/e* 318. An ir absorption at 1700 cm^{-1} indicated the presence

SCHEME I



of a carbonyl group in **2a** (Table I), which, on reduction with lithium aluminum hydride, was converted to the corresponding alcohol **3**. In the nmr spectrum, 2a revealed an AB-pattern quartet (8 H) centered at τ 6.35 assignable to methylene protons at C_2, C_7, C_{10}, and C_{11}, and a singlet (4 H) at τ 6.70 due to the ethano-bridge protons as well as a singlet (10 H) at τ 2.77 due to phenyl protons.

The mass spectral fragmentation pattern of **2a** was different from that of **1a**. Compound **2a** revealed some ion peaks corresponding to methyl piperidone and piperidine derivatives at *m/e* 268 and 251, although fragment peaks of pyridone derivatives at *m/e* 261, 260, and 247 are abundant for **1a**. An ion peak at *m/e* 58 appeared as a base peak for **2a**, while an ion peak at *m/e* 103 appeared for **1a**.

The methano bridge in **1a** is known to be cleaved very readily on treatment with acetic anhydride, affording *N,N'*-diacetylbispidin-9-one (**6b**).[7a] However, the same treatment of **2a** did not cleave the ethano bridge at all, even under more drastic conditions.

All of these spectral and chemical data are in good agreement with the assigned diphenyldiazahomoadamantanone structure for **2a**. The structural assignment of **2b** was performed similarly.

Spectral Properties.—In the uv spectra, **1a**, **1b**, **2a**, and **2b** all showed characteristic strong absorptions in the 224–260-nm region (Table I and Figure 1). An absorption of **1b** at 255 nm can be assigned to the σ-coupled (π–π^*) transition[3,4] that arises when the lone electron pair of nitrogen is antiperiplanar to the C_α–C_β bond of a carbonyl group. This absorption moves to shorter wavelengths on protonation of one of the nitrogen lone pairs in *ca.* 0.2 *N* ethanolic hydro-

(1) Part III of this series: T. Sasaki, S. Eguchi, and T. Kiriyama, *Tetrahedron Lett.*, 2651 (1971).

(2) (a) R. Hoffmann, A. Imamura, and W. J. Hehre, *J. Amer. Chem. Soc.*, **90**, 1499 (1968); (b) R. Hoffmann, *Accounts Chem. Res.*, **4**, 1 (1971); (c) W.-D. Stohrer and R. Hoffmann, *J. Amer. Chem. Soc.*, **94**, 779 (1972).

(3) R. C. Cookson, J. Henstock, and J. Hudec, *ibid.*, **88**, 1060 (1966).

(4) J. Hudec, *Chem. Commun.*, 829 (1970).

(5) (a) However, for the lone-pair σ_{cc} interactions in electrochemical oxidation of tertiary amines, see S. F. Nelson and P. J. Hintz, *J. Amer. Chem. Soc.*, **94**, 7114 (1972). (b) For the reactivity in the Grob fragmentation, see C. A. Grob, *Angew. Chem., Int. Ed. Engl.*, **8**, 535 (1969), and references cited therein; R. Gleiter, W.-D. Stohrer, and R. Hoffmann, *Helv. Chim. Acta*, **55**, 893 (1972).

(6) T. Sasaki, S. Eguchi, and T. Kiriyama, *J. Org. Chem.*, **36**, 2061 (1971).

(7) (a) H. Stetter, J. Schafer, and K. Dieminger, *Chem. Ber.*, **91**, 598 (1958); (b) J. Kutham and J. Palecock, *Collect. Czech. Chem. Commun.*, **28**, 2260 (1963); (c) S. Chiavarelli, F. Toffler, P. Mazzeo, and L. Gramiccioni, *Farmaco, Ed. Sci.*, **23**, 360 (1968).

(8) The ring-expansion reaction of adamantane derivatives is a general route to homoadamantane derivatives: R. C. Bingham and P. v. R. Schleyer, "Chemistry of Adamantanes," Springer-Verlag, New York, N. Y., 1971, p 30, and references cited therein. For azahomoadamantane, see T. Sasaki, S. Eguchi, and T. Toru, *J. Org. Chem.*, **35**, 4109 (1970), and references cited therein.

TABLE I

SPECTRAL PROPERTIES AND pK_a' VALUES OF 1,3-DIAZAADAMANTAN-6-ONE AND 3,6-DIAZAHOMOADAMANTAN-9-ONE DERIVATIVES

Compd	Uv, nm (ε) (EtOH)	Ir, cm^{-1} (KBr)	Nmr, τ ($CDCl_3$, 25°)	In H_2O (19°) pK_{a_1}'	In H_2O (19°) pK_{a_2}'
1a	250 (1640)	1700 (CO)	2.81 (m, 10, $2C_6H_5$), 5.82 (s, 2, NCH_2N), 6.25 (s, 8, other CH_2)	4.45	3.30
	(EtOH-HCl)[a-c]	(monohydrochloride)			
	249 (1130)	1728 (CO)			
	256 (1050)				
1b	255 (1380)	1694 (CO)	5.94 (s, 2, NCH_2N), 6.23 (s, 8, other CH_2),	5.15	3.43
		1725 ($COOCH_3$)	6.35 (s, 6, $COOCH_3$)		
	(EtOH-HCl)[a,c]				
	227 (1200)				
	(DMCS-HCl)[d]				
	224 (654)				
	285 (164)				
2a	250 (1840)[e]	1700 (CO)	2.77 (s, 10, $2C_6H_5$), 6.35 (AB q, 8,	5.03	3.46
	256 (1670)[e]		J = 14 Hz, $J/\Delta\tau$ = 0.486, $4CH_2$),		
	263 (1350)[e]		6.70 (s, 4, NCH_2CH_2N)		
	(EtOH-HCl)[a,c]	(dihydrochloride)			
	250 (1170)	1748			
	262 (1250)				
2b	259 (1670)	1696 (CO)	6.27 (s, 6, $2COOCH_3$), 6.83 (s, 4,	5.33	3.51
	(end type)	1725 ($COOCH_3$)	NCH_2CH_2N), 6.47 (AB q, 8, J = 14 Hz,		
			$J/\Delta\tau$ = 0.376, $4CH_2$)		
	(EtOH-HCl)[a,c]				
	259 (1000)				
	(DMCS-HCl)[d]				
	260–285[f]				
4	250 (1015)	1722 (CO)	4.25 (m, 10, $2C_6H_5$), 6.22 (s, 2, NCH_2NO),		
	256 (955)	970 (NO)	6.74 (AB q, 4, J = 12 Hz, $J/\Delta\tau$ =		
	262 (670)		0.364, $2CH_2$ at C_8 and C_9), 7.32 (s, 4,		
			$2CH_2$ at C_4 and C_{10})[g]		
5	250 (910)	1725 (CO)			
	256 (820)				
	263 (585)				
	285 (87, broad)				
8	250 (740)	3400 (OH)	2.55 (s, 10, $2C_6H_5$), 5.37 (s, 1, CHOH),	7.20	3.47
	256 (625)		5.95 (s, 2, NCH_2N), 6.05–6.90 (m, 8,		
	262 (425)		other CH_2), 7.45 (broad s, 1, OH)		

[a] *Ca.* 0.2 *N* hydrochloric acid in ethanol. [b] An ethanolic solution of the isolated monohydrochloride of **1a** gave the same absorptions. [c] No characteristic n–π* absorption was observed owing to the facile formation of diethyl ketal in *ca.* 1.5 *N* hydrochloric acid in ethanol. [d] Into dimethyl Cellosolve solution, dry hydrogen chloride gas was bubbled and the spectral change was followed by time. [e] As shoulder. [f] Because of lower solubility of **2b**, only broad weak absorption was observed qualitatively. [g] In CF_3COOH by using $CHCl_3$ as an internal reference.

chloric acid. The n–π* transition of a carbonyl group in these systems is too weak to be observed because of symmetry.[9] Further addition of hydrochloric acid until *ca.* 1.5 *N* ethanolic hydrochloric acid for complete protonation of both nitrogen lone pairs resulted in no unequivocal absorption in uv spectra.[10] However, in dimethyl Cellosolve saturated with dry hydrogen chloride, the carbonyl n–π* transition was observed at 285 nm (Table I). A similar absorption of σ-coupled transition for **1a** was observed, although the B band of the phenyl chromophore overlapped. However, the spectra of homoadamantane derivatives **2a** and **2b** were quite different from those of **1a** and **1b**, exhibiting only strong end absorption in this region. Addition of hydrochloric acid to the ethanolic solutions of **2a** and/or **2b** caused a dramatic change in the spectra: the broad

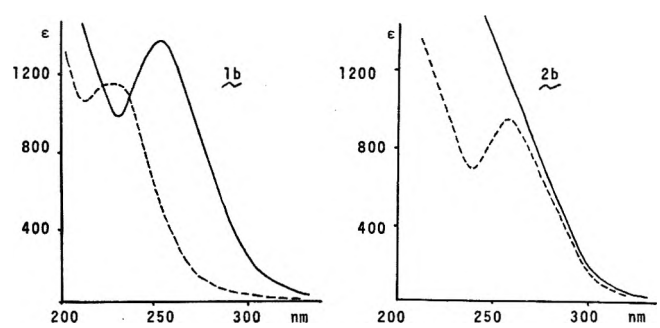


Figure 1.—Uv spectra of **1b** and **2b**: ——, in EtOH; ---, *ca.* 0.2 *N* hydrochloric acid in EtOH.

end absorption changed to an unequivocal peak at 259 nm for a monoprotonated derivative of **2b** and finally disappeared on further addition of hydrochloric acid;[10] a similar change was observed for **2a**, although the benzene B band overlapped in the same region.

(9) This phenomenon was also reported in symmetrical molecules such as tropinone; see ref 4.

(10) This is due to the formation of diethyl ketal in such a strongly acidic solution, as demonstrated by no characteristic carbonyl absorption in the ir spectrum and a molecular ion peak at *m/e* 342 in the mass spectrum.

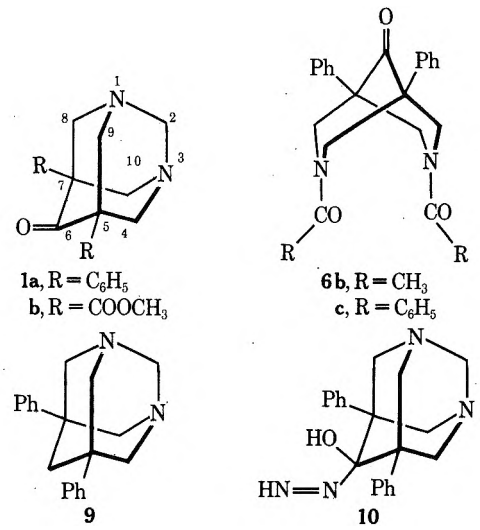
The broadening of the σ-coupled transition absorption of **2a** or **2b** is of interest in comparison with the relatively sharp absorption of **1a** or **1b**, since this difference suggests the presence of another through-σ-bond interaction between two lone electron pairs on two nitrogen atoms; the mixing of the interaction with the π orbitals on the carbonyl group may result in the splitting[2] of the σ-coupled transition of the β-amino ketone chromophore, and hence the broadening of the absorption. The interaction between two lone electron pairs on two nitrogen atoms in **2a** and **2b** should disappear on protonation of one of the nitrogen atoms. As the result, the spectra of **2a** and **2b** in weakly acidic solutions (*cf.* pK_a' values in Table I) showed the simple σ-coupled transition similar to those of **1a** and **1b**.[11-13]

In the ir spectra, **1a**, **1b**, **2a**, and **2b** showed considerably lower carbonyl stretching frequencies at around 1694–1700 cm^{-1} (Table I) compared to those of 4-piperidone derivatives,[14] while the corresponding hydrochlorides, trifluoroacetate, or some other derivatives such as **4** and **6a** had normal values. These facts suggest through-σ-bond interaction of the nitrogen lone electron pair with the carbonyl group in **1a**, **1b**, **2a**, and **2b** in the ground state, which is also supported by the basicity measurements as described below.

pK_a' Study.—The pK_a' values of **1a**, **1b**, **2a**, **2b**, and **8** were measured potentiometrically in water at 19° and the values obtained are summarized in Table I. The pK_{a_1}' values for the carbonyl compounds **1a**, **1b**, **2a**, and **2b** are considerably lower compared to that for alcohol **8**, though the pK_{a_2}' values are more or less similar for all compounds. Pseudopelletierine, with a similar piperidone system, has a pK_a' value of 7.55 in water,[15] which is also much higher than those of the present β-amino ketone derivatives.

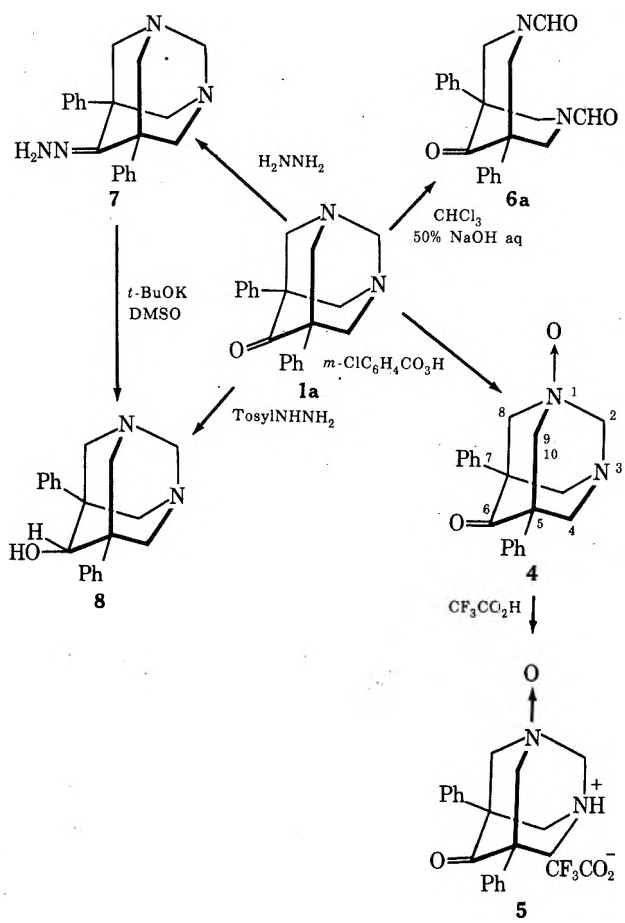
All of these spectral and pK_a' data indicate that β-amino ketone systems in **1a**, **1b**, **2a**, and **2b** should be regarded as an amide analog rather than independent *tert*-amine and keto groups. Therefore, examination of the carbonyl reactivity in these ring systems is of interest in connection with the structure–reactivity correlation.

Chemical Reactivity of 1a.—Reactions of **1a** with several carbonyl reagents were examined. Previously, the successful reductions of **1a** to alcohol **8** with $LiAlH_4$ or sodium alkoxide, and to amine **9** with hydrazine hydrate–sodium acetate, have been reported by Stetter[7a] as well as the facile ring fission to the bispidinones **6b** and **6c** with acetic anhydride and benzoyl chloride,



respectively. Some of the other reactions examined are summarized in Scheme II. As expected, **1a** did

SCHEME II



not react with the usual carbonyl reagents such as 2,4-dinitrophenylhydrazine and hydroxylamine, but with hydrazine hydrate **1a** gave the corresponding hydrazone **7** in a moderate yield only under very drastic conditions in refluxing diethylene glycol. With a large excess of

(11) The through-σ-bond interaction between two nitrogen atoms is expected to be operative effectively only in an eclipsed conformation of the ethano bridge in **2a** and **2b**; *cf.* ref 2.

(12) The untwisted conformation of the NCH_2CH_2N group in **2a** was suggested by the nmr spectra, since the protons of the ethano bridge at τ 6.70 exhibited no broadening on cooling until at −70° in CH_2Cl_2. The nmr measurement at below −70° was unsuccessful because of the lower solubility of **2a**. Furthermore, **2a** and **2b** had J_{gem} of 14 Hz for CH_2 at C_2, C_7, C_{10}, and C_{11}. This larger J_{gem} value of the homoadamantane system compared to those of the adamantane series (mono-*N*-oxide **4**, for example, had J_{gem} = 12 Hz) is indicative of somewhat flattened cyelohexane ring structures in **2a** and **2b**; for detailed nmr studies on related azacyclic compounds, see (a) S. P. Nelsen, P. J. Hintz, and R. T. Landis, II, *J. Amer. Chem. Soc.*, **94**, 7105 (1972); (b) R. C. Cookson, T. A. Crabb, J. J. Frankel, and J. Hudee, *Tetrahedron, Suppl.*, **No. 7**, 355 (1966).

(13) Homoadamantane itself has been reported recently to have a broad energy minimum between skewing angles of ±33° from calculations; E. M. Engler, L. Chang, and P. v. R. Schleyer, *Tetrahedron Lett.*, 2525 (1972). For the preferred untwisted conformation of *cis*-4,5-homoadamantandiol and homoadamantan-4,5-dione, see P. v. R. Schleyer, E. Funke, and S. H. Liggero, *J. Amer. Chem. Soc.*, **91**, 3965 (1969); J. L. M. A. Schlatmann, J. G. Korsloot, and J. Schut, *Tetrahedron*, **26**, 949 (1970).

(14) For example, *N*-methyl-4-piperidone has a carbonyl frequency at 1725 cm^{-1}: C. J. Pouchert, "The Aldrich Library of Infrared Spectra," Aldrich Chemical Co., Inc., 1970.

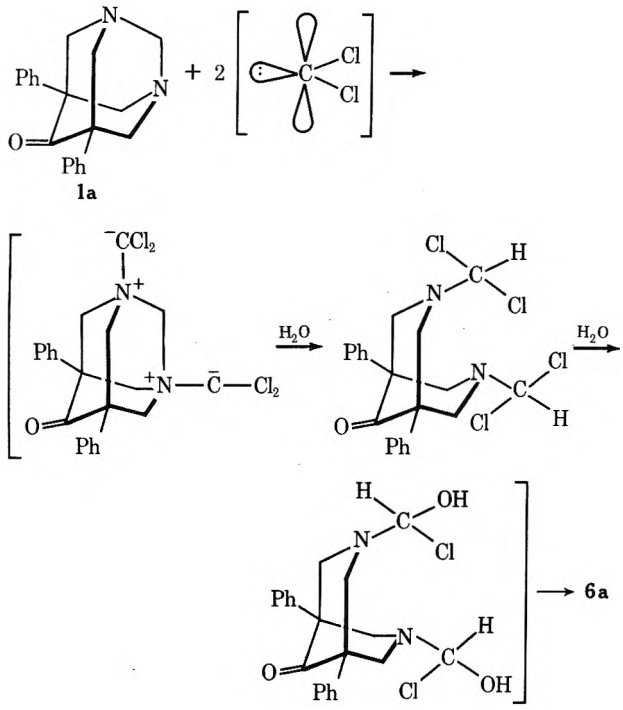
(15) T. Sasaki, S. Euchi, and T. Kiriyama, *Bull. Chem. Soc. Jap.*, **44**, 3410 (1971).

diazomethane, **1a** did not react at all. These facts point to a lower reactivity of the carbonyl group; however, steric hindrance by the 5,7-diphenyl substituents is considered to be another reason.[16]

Reaction of **1a** with excess *m*-chloroperbenzoic acid or hydrogen peroxide afforded no Baeyer–Villiger product but only mono-*N*-oxide **4**. The mono-*N*-oxide structure of **4** was supported by the formation of the monotrifluoroacetate **5**.

Reaction of **1a** with dichlorocarbene in an alkaline micelle[17] afforded a ring-fission product, 1,5-diphenyl-*N*,*N'*-diformylbispidinone (**6a**). The formation of **6a** could be explained by an initial attack of dichlorocarbene on nitrogen followed by ring fission and hydrolysis as illustrated in Scheme III.

SCHEME III



When a mixture of *p*-toluenesulfonylhydrazide (tosylhydrazide), **1a**, and barium oxide in ethanol was heated at 65°, no trace of the corresponding tosylhydrazone was produced but alcohol **8** was produced in a low yield. The formation of **8** from **1a** and tosylhydrazide can be explained reasonably by diimide type reduction or by decomposition of a hydroxyazene intermediate (**10**).[18–20] This is the first example of novel reduction of a very inert alicyclic ketone with tosylhydrazide, though an example for an aromatic ketone has been reported.[20]

When **7** was treated with potassium *tert*-butoxide in dimethyl sulfoxide, only alcohol **8** was produced but no Wolff–Kishner reduction product **9**. This reaction might proceed similarly as above *via* diimide type reduction.

These results on the facile formation of **8** are in good accord with the expected lower reactivity of the carbonyl group in **1a**.

(16) The ready formation of the diethyl ketal of **2a** in strongly acidic ethanol suggests that the steric hindrance of 5,7-diphenyl substituents is not extremely severe; see ref 10.

(17) M. Makosza and M. Warzyniewiez, *Tetrahedron Lett.*, 4659 (1969).

(18) For reviews on diimide reductions, see (a) A. Furst, R. C. Berlo, and S. Hooton, *Chem. Rev.*, **65**, 51 (1965); (b) S. Hunig, H. R. Miller, and W. Thier, *Angew. Chem.*, **77**, 368 (1965); (c) C. E. Miller, *J. Chem. Educ.*, **42**, 254 (1965); (d) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, p 248.

(19) For the formation of diimide from tosylhydrazide, see R. S. Dewery and E. E. van Tamelen, *J. Amer. Chem. Soc.*, **83**, 3729 (1961).

(20) For an example of such a novel reduction of a very inert aromatic ketone with tosylhydrazide, see J. J. Looker, *J. Org. Chem.*, **32**, 472 (1967).

Experimental Section[21]

5,7-Diphenyl-1,3-diazaadamantan-6-one (1a).—This was prepared by the known method:[7a] mp 255–258° (lit.[7a] mp 257°); mass spectrum *m/e* (rel intensity) 304 (13, M^+), 261 (43), 260 (12), 247 (10), 233 (15), 146 (13), 144 (18), 131 (42), 103 (100), 91 (33), 77 (36), 57 (35), and 42 (65).

5,7-Dicarbomethoxy-1,3-diazaadamantan-6-one (1b).—A mixture of ammonium acetate (5.00 g, 65.0 mmol), dimethyl acetonedicarboxylate (3.58 g, 20.0 mmol), and paraformaldehyde (3.28 g, 108 mmol) in ethanol (30 ml) was refluxed for 3 hr. Removal of the solvent and extraction with benzene (5 × 20 ml) followed by evaporation afforded a solid product which was recrystallized from ethanol–benzene to give **1b** as colorless crystals (340 mg, 6.4%): mp 175–177°; mass spectrum *m/e* (rel intensity) 268 (7, M^+), 241 (14), 240 (30), 239 (15), 237 (41), 226 (13), 209 (15), 208 (22), 194 (18), 181 (12), 177 (18), 167 (8), 142 (6), 140 (8), 114 (12), 113 (100), 96 (26), 69 (12), 59 (74), and 57 (93).

Anal. Calcd for $C_{12}H_{16}N_2O_5$: C, 53.72; H, 6.01; N, 10.44. Found: C, 53.91; H, 6.00; N, 10.26.

1,8-Diphenyl-3,6-diazahomoadamantan-9-one (2a).—A mixture of dibenzyl ketone (4.20 g, 20.0 mmol), paraformaldehyde (3.60 g, 120 mmol), and ethylenediammonium diacetate (3.60 g, 30.0 mmol) prepared from ethylenediamine and acetic acid in ethanol (30 ml) was refluxed for 1 day. After removal of the solvent, the crude product was extracted with benzene (5 × 20 ml) and the combined benzene extracts were purified on a silica gel column eluting with a $CHCl_3$–EtOH system to afford **2a** as colorless crystals (510 mg, 8.1%): mp 182–185°; mass spectrum *m/e* (rel intensity) 318 (72, M^+), 287 (15), 268 (15), 251 (10), 240 (15), 160 (62), 117 (33), 113 (41), 103 (71), 77 (42), and 58 (100).

Anal. Calcd for $C_{21}H_{22}N_2O$: C, 79.21; H, 6.96; N, 8.80. Found: C, 79.44; H, 7.04; N, 8.59.

1,8-Dicarbomethoxy-3,6-diazahomoadamantan-9-one (2b).—A mixture of ethylenediammonium diacetate (4.32 g, 24.0 mmol), dimethyl acetonedicarboxylate (3.48 g, 20 mmol), and paraformaldehyde (3.60 g, 120 mmol) in methanol (30 ml) was refluxed for 20 hr. After removal of the solvent, the crude product was extracted with benzene (5 × 20 ml) and the benzene extract was washed once with 10% aqueous sodium carbonate and dried (Na_2SO_4). Removal of the solvent and recrystallization from carbon tetrachloride afforded **2b** as colorless crystals (310 mg, 5.7%): mp 134–135°; mass spectrum *m/e* (rel intensity) 282 (20, M^+), 251 (10), 241 (5), 240 (5), 226 (8), 223 (6), 218 (6), 195 (5), 183 (5), 180 (5), 167 (5), 153 (5), 152 (6), 150 (8), 142 (11), 140 (10), 126 (10), 113 (51), 69 (28), 59 (69), 57 (70), and 43 (100).

Anal. Calcd for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.43; N, 9.92. Found: C, 55.23; H, 6.29; N, 9.66.

1,8-Diphenyl-3,6-diazahomoadamantan-9-ol (3).—A mixture of **2a** (170 mg, 0.530 mmol) and lithium aluminum hydride (30 mg, 0.79 mmol) in dry tetrahydrofuran (20 ml) was refluxed for 4 hr. The excess reagent was decomposed by adding water (50 ml) and the mixture was extracted with methylene chloride (5 × 20 ml) and dried (Na_2SO_4). Removal of the solvent and recrystallization from methanol afforded **3** as colorless crystals (120 mg, 75%): mp 233–237°; ir (KBr) 3400 cm^{-1}; nmr ($CDCl_3$) τ 2.72 (s, 10, 2 C_6H_5), 5.42 (s, 1, C_9H), 6.18 (d of d, 2, J = 14 and 3 Hz, C_7H_{ax} and $C_{10}H_{ax}$ anti to OH), 6.79 (s, 4, NCH_2CH_2N), 7.20 (d, 4, J = 14 Hz, C_2H_{eq}, C_7H_{eq}, $C_{10}H_{eq}$, and $C_{11}H_{eq}$), and 7.95 (s, 1, OH); mass spectrum *m/e* (rel intensity) 320 (100, M^+), 303 (30), 291 (35), 248 (21), 246 (17), 232 (22), 231 (24), 217 (30), 160 (37), 111 (35), 97 (50), 85 (53), and 83 (43).

(21) All melting points were obtained on a hot-stage type Yanagimoto micromelting point apparatus and are uncorrected. Nmr spectra were recorded on a JEOL JNM-C-60HL spectrometer at 60 MHz and mass spectra on a JEOL JMS-01SG mass spectrometer at 75 eV. Ir spectra were obtained with a JASCO IR-S spectrometer and uv spectra on a JASCO ORD/UV-5 spectrometer. Microanalyses were carried out with a Perkin-Elmer 240 Elemental Analyzer.

Anal. Calcd for $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.74. Found: C, 78.42; H, 7.55; N, 8.45.

5,7-Diphenyl-1,3-diazaadamantan-6-one *N*-Oxide (4).—A mixture of **1a** (300 mg, 0.987 mmol) and *m*-chloroperbenzoic acid (520 mg, 3.00 mmol) in chloroform (20 ml) was refluxed for 13 hr. After cooling, excess peracid was decomposed by adding 10% aqueous sodium bisulfite solution and the mixture was extracted with 10% aqueous sodium carbonate solution (3 × 10 ml). The organic layer was dried (Na_2SO_4) and the solvent was removed to afford a crude product which was purified on a silica gel column eluting with a $CHCl_3$–EtOH system to give **4** as colorless crystals (100 mg, 32%): mp 258–261°; mass spectrum *m/e* (rel intensity) 320 (12, M^+), 304 (72), 261 (100), 260 (57), 247 (24), 233 (24), 159 (19), 144 (23), 131 (32), and 103 (46). Treatment of **4** with trifluoroacetic acid gave quantitatively trifluoroacetate salt **5**: mp 177–181°; ir (KBr) 1725 (CO), 1670 (COO^-), and 1190 cm^{-1} (CF_3).

Anal. Calcd for $C_{22}H_{21}N_2O_4F_3$: C, 52.76; H, 3.69; N, 5.12. Found: C, 52.81; H, 3.93; N, 5.12.

***N,N'*-Diformylbispidin-9-one (6a).**—To a vigorously stirred mixture of **1a** (300 mg, 0.987 mmol), triethylbenzylammonium chloride (20 mg, 0.088 mmol), benzene (5 ml), and 50% sodium hydroxide aqueous solution (10 ml) was added dropwise a mixture of benzene (5 ml) and chloroform (0.80 ml, 9.9 mmol) at 25° in *ca.* 0.5 hr. After the addition was completed, the stirring was continued for a further 22 hr, and the mixture was diluted with water (60 ml) and extracted with chloroform (2 × 30 ml). The combined extracts were dried (Na_2SO_4) and evaporated to give a crude product, which was chromatographed on a silica gel column ($CHCl_3$–EtOH) to afford **6a** as colorless crystals (80 mg, 23%): mp 229–232°; ir (KBr) 1720 (CO) and 1680 cm^{-1} (NCHO); nmr ($CDCl_3$) τ 1.98 (s, 2, 2 CHO), 2.69 (s, 10, 2 C_6H_5), 4.80 (d of d, 2, J = 13 and 2 Hz, C_2H_{eq} anti to oxygen atom of the formyl carbonyl), 5.95 (AB q, 4, J = 13 Hz, $J/\Delta\tau$ = 0.542, 2 CH_2 at C_4 and C_8 syn to oxygen atom of the formyl carbonyl), and 6.55 (d of d, 2, J = 13 and 2 Hz, C_2H_{ax} and C_6H_{ax} anti to the formyl carbonyl);[22] mass spectrum *m/e* (rel intensity) 348 (100, M^+), 320 (36), 277 (73), 276 (95), 248 (32), 233 (26), 207 (34), 205 (32), 105 (62), 103 (51), 97 (41), 85 (41), 83 (45), 71 (57), 69 (47), 57 (95), 44 (53), 43 (85), 41 (42), and 40 (38).

Anal. Calcd for $C_{21}H_{20}N_2O_3$: C, 72.39; H, 5.79; N, 8.04. Found: C, 72.40; H, 6.04; N, 7.88.

5,7-Diphenyl-1,3-diazaadamantan-6-one Hydrazone (7).—A mixture of **1a** (600 mg, 1.97 mmol) and 80% hydrazine hydrate (5.00 g, 80.0 mmol) in diethylene glycol (20 ml) was refluxed with a Dean–Stark trap for 18 hr. The cooled mixture was diluted with water (50 ml) and extracted with chloroform (20 ml). The extract was washed with water (2 × 10 ml) and dried (Na_2SO_4). Removal of the solvent and chromatography of the crude product on a silica gel column ($CHCl_3$–EtOH) afforded **7** as colorless crystals (390 mg, 62%): mp 249–251°; mass spectrum *m/e* (rel intensity) 318 (19, M^+), 275 (32), 247 (14), 223 (15), 205 (14), 175 (13), 150 (34), 141 (15), 119 (13), 105 (13), 104 (20), 97 (14), 95 (12), 93 (13), 91 (14), 85 (17), 83 (17), 81 (14), 76 (20), 71 (30), 69 (26), 57 (70), 56 (40), 55 (34), 44 (32), 43 (32), 41 (62), and 40 (100); ir (KBr) 3425 and 3305 cm^{-1}; nmr ($CDCl_3$) τ 2.65 (s, 5, C_6H_5), 2.83 (s, 5, C_6H_5), 5.70 (s, 2, disappeared on deuteration, NH_2), 5.89 (s, NCH_2N), 6.15 (d of d, 4, J = 12 and 4 Hz, C_4H_{ax}, C_8H_{ax}, C_9H_{ax}, and $C_{10}H_{ax}$), and 6.53 (d of d, 4, J = 12 and 3 Hz, C_4H_{eq}, C_8H_{eq}, C_9H_{eq}, and $C_{10}H_{eq}$).

Anal. Calcd for $C_{20}H_{22}N_4$: C, 75.44; H, 6.96; N, 17.60. Found: C, 75.21; H, 6.96; N, 17.82.

Reaction of 1a with Tosylhydrazide.—A mixture of **1a** (160 mg, 0.83 mmol), tosylhydrazide (200 mg, 1.08 mmol), and barium oxide (2.0 g, 13.1 mmol) in ethanol was heated at 65° with occasional stirring for 3 days. After removal of the solids by filtration, the filtrate was evaporated to dryness to give crude product, which on purification by preparative tlc (silica gel, 5% MeOH–$CHCl_3$) afforded recovered **1a** (110 mg, 80% recovery) and 5,7-diphenyl-1,3-diazaadamantan-6-ol (**8**) (30 mg, 20%), mp 282–284° (lit.[7a] mp 274°), identified by spectral (ir and nmr) comparison with an authentic sample.[7a]

Treatment of 7 with Potassium *tert*-Butoxide in Dimethyl Sulfoxide.—To a solution of potassium *tert*-butoxide (40 mg, 0.36 mmol) in freshly distilled (from KOH) dimethyl sulfoxide (4 ml) was added **7** (60 mg, 0.19 mmol) and the resulting solution was stirred for 22 hr at room temperature under nitrogen atmosphere. The mixture was poured onto ice–water (30 ml) and extracted with methylene chloride (4 × 20 ml). The combined extracts were dried (Na_2SO_4) and evaporated to afford **8** (47 mg, 80%).

pK_a' Measurements.—pK_a' measurements were carried out by titrating potentiometrically an acidic solution of each amine (prepared by dissolving *ca.* 2.5 mg of amine into 3.00 ml of 0.01 *N* hydrochloric acid) with 0.1 *N* potassium hydroxide aqueous solution at 19°. The titration was performed on a Radiometer Model TT1.

Registry No.—**1a**, 19066-35-4; **1b**, 38740-11-3; **2a**, 38740-12-4; **2b**, 38740-13-5; **3**, 38740-14-6; **4**, 38740-15-7; **5**, 38740-16-8; **6a**, 38740-17-9; **7**, 38740-18-0; **8**, 3576-75-8; ammonium acetate, 631-61-8; dimethyl acetonedicarboxylate, 1830-54-2; dibenzyl ketone, 1083-30-3; ethylenediammonium acetate, 38734-69-9; trifluoroacetic acid, 76-05-1; tosylhydrazide, 1576-35-8.

(22) The formyl group seems to rotate not freely at room temperature, and hence two formyl groups in **6a** take preferably the anti conformation to each other by dipole–dipole interaction, though further details on this problem will be published elsewhere: *cf.* ref 6 and references cited therein.

Azodicarboxylic Acid Esters as Dealkylating Agents[1]

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The use of azodicarboxylic acid esters as dealkylating agents has been studied. The isolation and structure proof of the intermediate adducts obtained from the reaction of the azo esters with secondary and tertiary amines is reported. Dealkylation of compounds other than amines by this method is also discussed.

The diesters of azodicarboxylic acid (**1**, **2**) react with aliphatic primary amines to give amides,[2-4] while primary aromatic amines yield either triazan addition compounds[4-6] or ring-substituted systems.[6,7] It was reported that whereas piperidine reacts with diethyl azodicarboxylate (**1**) to yield the corresponding azodicarboxamide, other secondary amines combined with one molecule of this ester to give a stable addition product.[3,4] On acidic hydrolysis these adducts produced aldehydes in relatively low yields. Diels[3] assigned structure **3** to these adducts and later Kenner and Stedman,[8] utilizing infrared evidence, proposed the triazan structure **4**.

Diels was the first to investigate the reaction of the

(1) Taken in part from the dissertation presented by A. Makriyannis, March 1967, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy degree.

(2) O. Diels, *Justus Liebigs Ann. Chem.*, **429**, 1 (1922).

(3) O. Diels and M. Paquin, *Chem. Ber.*, **46**, 2000 (1913).

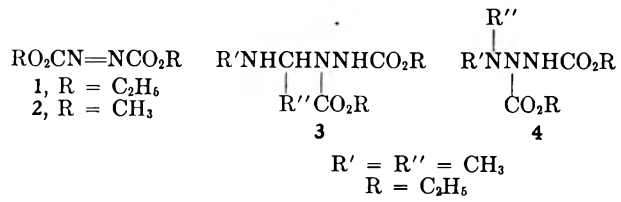
(4) O. Diels and P. Fritzsche, *ibid.*, **44**, 3018 (1911).

(5) K. E. Cooper and E. H. Ingold, *J. Chem. Soc.*, 1894 (1926).

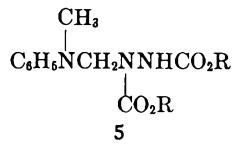
(6) G. S. Misra and S. B. Srivastava, *J. Indian Chem. Soc.*, **37**, 177 (1960).

(7) O. Diels, *Chem. Ber.*, **54**, 213 (1921).

(8) G. W. Kenner and R. J. Stedman, *J. Chem. Soc.*, 2089 (1952).

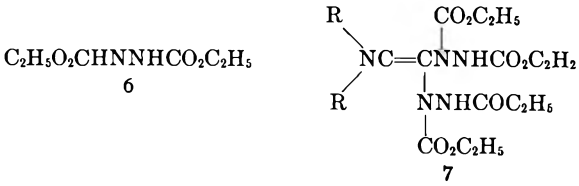


azodicarboxylic acid esters with tertiary alkylamines.[3,4] When *N*,*N*-dimethylaniline was used, a compound corresponding to the addition of one molecule of amine to one molecule of the azo ester was obtained. On acidic hydrolysis he obtained the corresponding monodemethylated amine and formaldehyde. He favored structure **5** as representing the adduct. Kenner



and Stedman[8] provided evidence to substantiate this proposed structure and suggested that its formation involved initial coordination of the basic nitrogen atom with the electrophilic azo group followed by a two-step ylide rearrangement. Huisgen and Jakob[9] provided some evidence in support of a similar mechanism.

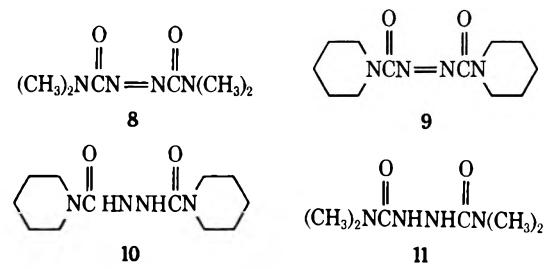
Tertiary amines containing the CHCHN– grouping were recently reported[10] to react with **1** in two steps through a different mechanism. In the first step a dehydrogenation takes place leading to diethyl hydrazodicarboxylate (**6**) and the corresponding enamines. The enamines can then react further with **1**, yielding the corresponding mono- or diadducts (**7**) which can



hydrolyze readily in acidic media to the secondary amines.

In these laboratories an investigation of the use of azodicarboxylic acid esters as dealkylating agents led to the isolation and conclusive structure proof of the adducts obtained from the reaction of the azo ester with secondary or tertiary amines. The investigation also provided information for the determination of the relative ease of dealkylation of unsymmetrically substituted tertiary aliphatic amines. A further study as to the possibility of using azo esters to dealkylate ethers and thio ethers was also performed.

Reaction with Secondary Amines.—When either **1** or **2** was allowed to react with a solution of dimethylamine or piperidine in ether, the reaction occurred at the ester carbonyl carbon of the azo ester, giving rise to *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (**8**) and azodicarboxyldipiperidide (**9**), respectively. When dimethylamine was mixed with **2** in a methanol–ether (1:1) or an ethanol–ether (1:1) solution, **8** was the only product isolated. However, when **1** was used under similar conditions the diamide **8** was only a minor product. The major product resulted from reaction at the azo nitrogen. This colorless addition product was characterized from its infrared and nmr spectra as diethyl 1,1-dimethyltriazane-2,3-dicarboxylate (**4**), the structure suggested by Kenner and Stedman. Piperidine yielded only the diamide **9** with both esters.



Following the failure to obtain the piperidyl adduct of the azo ester, the piperidyl adduct of **9** was sought. Reaction of **9**, however, with excess piperidine either by refluxing or by allowing the mixture to stand at room temperature for 1 week afforded a crystalline product identified as hydrazodicarboxyldipiperidide (**10**).

The difference in reactivity between **1** and **2** can be attributed to the larger steric effects operating at the carbonyl reaction center in the case of **1**. Piperidine, on the other hand, owing to its considerable bulk, was incapable of reacting with the azo nitrogen even under severe conditions.

The nmr spectrum of **8** in deuteriochloroform consisted of two sharp singlets at δ 3.00 and 3.12 ($\Delta\delta_{AB}$ 0.12) each due to six protons. Furthermore the nmr spectrum of **9** in carbon tetrachloride showed the presence of two equivalent, partially overlapping broad peaks at δ 3.15–3.77 ($\Delta\delta_{AB}$ 0.27) due to the methylene groups α to the amido nitrogen. When the solvent was changed to benzene a strong general upfield shift of the peaks was observed. The magnitude of this upfield shift was distinctly larger with the singlet situated higher upfield ($\Delta\delta_{AB}$ 0.20) in the case of **8** as well as with the broad peak situated higher upfield ($\Delta\delta_{AB}$ 0.31) in the case of **9**.

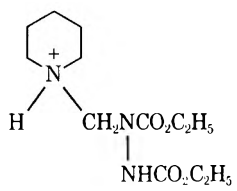
The observations mentioned above constitute evidence for the nonequivalence of the amide alkyl groups and indicate some conformational rigidity in the system. Similar observations concerning the nonequivalence of the two methyl groups in *N*,*N*-dimethylamides have been reported.[11,12]

Examination of the nmr spectrum of **10** in deuteriochloroform revealed that there was only one broad peak (δ 3.24–3.62) due to the four methylene protons α to the amido nitrogen. This observation, in conjunction with the absence of any significant solvent effect, provides evidence for a lack of conformational rigidity in this system.

Reaction with Tertiary Amines.—When *N*-methylpiperidine was allowed to react with **2**, a white, crystalline compound was isolated from the reaction mixture. The elemental analysis of the compound was compatible with a structure obtained from the addition of one

(9) R. Huisgen and F. Jakob, *Justus Liebigs Ann. Chem.*, **590**, 37 (1954).
(10) M. Colonna and L. Marchetti, *Gazz. Chim. Ital.*, **99**, 14 (1969).
(11) J. V. Hatton and R. E. Richards, *Mol. Phys.*, **5**, 153 (1962).
(12) L. A. LaPlanche and M. T. Rogers, *J. Amer. Chem. Soc.*, **86**, 337 (1964).

molecule of the amine to one of the azo ester. Acid hydrolysis of the compounds afforded equimolar amounts of formaldehyde, piperidine, and dimethyl hydrazodicarboxylate. The infrared spectrum of the compound showed absorptions at 3350, 1740, and 1750 cm^{-1}, indicating the presence of an NH group and two nonequivalent carbonyl groups. The nmr spectrum furnished conclusive evidence that the isolated adduct was diethyl *N*-(piperidinomethyl)-hydrazine-*N*,*N*′-dicarboxylate. The product obtained from the reaction between **1** and *N*-methylpiperidine, when isolated as its hydrochloride salt, was identified by infrared and nmr analysis as diethyl *N*-(piperidinomethyl)hydrazine-*N*,*N*′-dicarboxylate hydrochloride (**12**).



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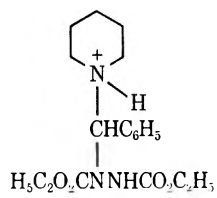

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N-Benzylpiperidine, when allowed to react with **1**, afforded an adduct whose hydrochloride salt was identified as diethyl *N*-(piperidinobenzyl)hydrazine-*N*,*N*′-dicarboxylate hydrochloride (**13**). This compound was extremely hygroscopic and labile, hydrolyzing spontaneously into equimolar amounts of benzaldehyde, piperidine, and **6**.

The relative ease of dealkylation of the different alkyl groups was determined by performing the reaction on a number of unsymmetrically substituted tertiary amines (Table I).

TABLE I

DEALKYLATION OF TERTIARY AMINES USING DIETHYL AZODICARBOXYLATE[a]

	Dealkylation, %		
Amine	CH_3	C_2H_5 or C_3H_5	$C_6H_5CH_2$
N,*N*-Diethylmethylamine	14	83	
N-Methylpiperidine	73		
N-Ethylpiperidine		83	
N-Benzylpiperidine			91
N,*N*-Dimethylbenzylamine[b]	11		89
N,*N*-Diethylbenzylamine		67	33
N,*N*-Di-*n*-propylbenzylamine		56	38
N,*N*-Diisopropylbenzylamine		48	52

[a] It was found that there was no significant difference in these results when **2** was used instead of **1**. [b] The results of the dealkylation of *N*,*N*-dimethylbenzylamine shown here differ sharply from those reported by Kenner and Stedman.[8] Those investigators using dibenzyl azodicarboxylate reported only the adduct resulting from the reaction of a methyl group of the tertiary amine.

The effect of ring substitution on the reactivity of the benzyl group was studied by allowing a number of ring-substituted *N*,*N*′-diethylbenzylamines to react with **1** (Table II).

In every case the reaction mixture was analyzed by gas–liquid chromatography to determine the amounts of the different secondary amines obtained from the dealkylation of the corresponding tertiary amine.

TABLE II

DEALKYLATION OF SUBSTITUTED *N*,*N*-DIETHYLBENZYLAMINES USING DIETHYL AZODICARBOXYLATE

Substituent	Debenzylation, %
p-H	33
p-OCH_3	55
p-CH_3	39
p-Cl	40
p-NO_2	96

In the case of disubstituted benzylamines the amount of debenzylation could also be determined by measuring the amount of benzaldehyde obtained.

The method of analysis was based on the observation that when an aqueous solution of the tertiary amine–azo ester hydrochloride salt adduct was injected into a gas chromatograph having a hot injection port (220–240°), spontaneous hydrolysis of the adducts occurred. This method of analysis proved satisfactory when tested on standards.

The overall rate of the reaction between the azo esters and the tertiary amines[13] appeared to be greatly affected by the nucleophilicity of the latter. The reactivity of *N*,*N*′-dialkylbenzylamines decreased with an increase in the bulk of the alkyl substituents in the following order: isopropyl < *n*-propyl < Et < Me. The same was observed with the substituted piperidines, where benzyl < Et, Me. The para-substituted *N*,*N*′-diethylbenzylamines reacted in the order OCH_3 > CH_3, H > Cl > NO_2, the more basic amines reacting faster.

The reaction of the tertiary amine alkyl groups with azodicarboxylate esters proceeds by two different mechanisms depending on the presence or absence of alkyl hydrogens β to the amino nitrogen. They appear to have a common first step: the nucleophilic attack of the amino nitrogen on the azo group.

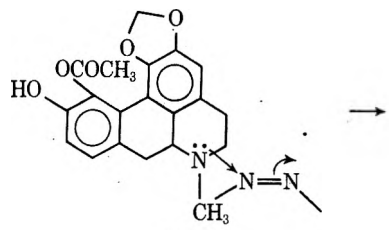
Preferential demethylation occurred only in the case of *N*-methylpiperidine, where ring dehydrogenation is less favored, probably because of stereoelectric considerations.[10]

The comparison of the reactivity of the benzylic position in para-substituted *N*,*N*-diethylbenzylamines does not present a clear picture of the electronic factors involved in this reaction. However, the fact that the *p*-nitro compound possesses by far the most reactive benzylic position is compatible with the suggested ylide intermediate.[8,9]

When *O*-acetyl bulbocapnine (**14**) was allowed to react with **1**, a pale, crystalline compound insoluble in dilute acid and alkali was obtained. When the compound was subjected to hydrolysis with dilute sulfuric acid, only the *O*-acetyl group was cleaved to give the free phenol while the remainder of the molecule remained intact. Based on further infrared and nmr evidence the product of this reaction, which probably proceeded through the mechanism outlined below, was identified as 1-[2-[(*N*,*N*′-dicarbethoxyhydrazino)-methylamine]ethyl]-3,4-methylenedioxy-5-acetoxy-6-methoxyphenanthrene (**15**).

Reaction with Ethers and Thioethers.—A study of the dealkylation of ethers and thioethers was initiated. The reactions of **1** with dibenzyl ether and dibenzyl

(13) The relative reactivities of the tertiary amines were based on their observed reaction times with the azo esters.



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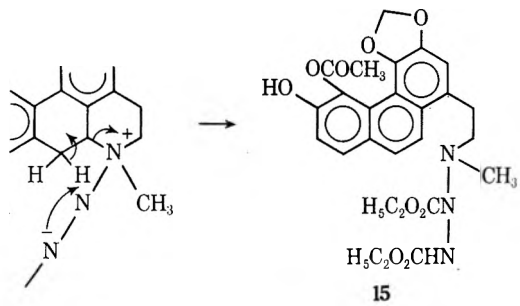

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thioether were performed in the absence of solvent. It was found that heating to 100° was sufficient to initiate the reaction, no ultraviolet irradiation being necessary.[14,15] The free radicals appear to originate from the thermal decomposition of the azo ester. Both adducts obtained (**17**, **18**) were labile in the presence of moisture.

$$C_6H_5HCXCH_2C_6H_5$$
$$|$$
$$NCO_2C_2H_5$$
$$|$$
$$NHCO_2C_2H_5$$

16, X = O
17, X = S

The method of analysis of the products was based on the observation that when an acidic solution of the adduct was injected into a gas chromatograph having a hot injection port (220–240°), complete spontaneous hydrolysis occurred. Determination of the benzaldehyde obtained from these reaction mixtures indicated that the dealkylations occurred quantitatively.

Experimental Section[16]

***N,N,N′,N′*-Tetramethylazodicarboxamide** (**8**).—To a cooled solution of diethyl azodicarboxylate (1, 1.00 g, 5.74 mmol) in 20 ml of anhydrous Et_2O, Me_2NH (0.50 g, 11.09 mmol) was added slowly with continuous stirring. The mixture was allowed to stand at 0° for 2 hr and the yellow flakes which formed were filtered and washed with a small amount of anhydrous Et_2O. The filtrate was concentrated to a volume of 10 ml and allowed to stand at 0° for 12 hr. A second crop of crystals was filtered and washed with a small amount of anhydrous Et_2O. The combined crops of the product were recrystallized [*n*-hexane–C_6H_6 (10:1)] to give long, bright yellow needles (0.78 g, 4.53 mmol, 79%): mp 111–112°; ir (KBr) 1700 cm^{-1} (C=O) [lit.[17] 1701 cm^{-1} (Nujol)]; nmr ($CDCl_3$) δ 3.00 and 3.12 (2 s).

Anal. Calcd for $C_6H_{12}N_4O_2$: C, 41.85; H, 7.02; N, 32.54. Found: C, 41.76; H, 6.93; N, 32.84.

Azodicarboxyldipiperidide (**9**).—To a cooled solution of diethyl azodicarboxylate (1, 1.00 g, 5.74 mmol) in 30 ml of anhydrous Et_2O, piperidine (1.00 g, 11.74 mmol) was added dropwise with continuous stirring. The mixture was allowed to stand at 0° for 2 hr and the crystals which formed were filtered and washed with a small amount of Et_2O (anhydrous). The filtrate was concentrated to 8 ml and allowed to stand at 0° for 15 hr. The second crop of crystals was filtered and washed with a small amount of Et_2O (anhydrous). The combined product was recrystallized [*n*-hexane–C_6H_6 (10:1)] to give golden yellow crystals (0.92 g, 3.65 mmol, 64%): mp 135° (lit.[4] mp 134–135°); ir (KBr) 1705 cm^{-1} (C=O) [lit.[17] 1704 cm^{-1} (KBr)]; nmr (CCl_4) δ 3.15–3.77 (two partially overlapping broad peaks, 8 H, CH_2NCH_2), 1.47–1.88 (broad peak, 12 H, $CCH_2CH_2CH_2C$).

Anal. Calcd for $C_{12}H_{20}N_4O_2$: C, 57.14; H, 7.94; N, 22.22. Found: 57.12; H, 7.84; N, 22.14.

Diethyl 1,1-Dimethyltriazan-2,3-dicarboxylate (**4**).—This substance was prepared as by Diels and Paquin[3] and was recrystallized [*n*-hexane–C_6H_6 (15:1)]: mp 94–95° (lit. mp 92.5–93°,[8] 95°[3]); ir (KBr) 3260 (NH), 1760 (C=O), 1690 cm^{-1} (C=O); nmr ($CDCl_3$) δ 6.91 (broad peak, NH), 4.14 and 4.16 (2 q overlapping 8, J = 7.5 cps, 4 H, CO_2CH_2), 2.54 (s, 6 H, $N(CH_3)_2$], 1.30 (t, 6 H, CCH_3).

***N,N,N′,N′*-Tetramethylhydrazodicarboxamide** (**11**).—A solution of **8** (2.00 g, 11.61 mmol) in methanol (30 ml, anhydrous) was hydrogenated for 15 min at 50 psi using platinum oxide (20 mg) as a catalyst. After filtration and removal of the solvent, a white, crystalline residue was obtained which was purified by recrystallization (Me_2CO) to give colorless crystals (1.95 g, 11.20 mmol, 97%): mp 221° (lit.[18] mp 220–221°); ir (KBr) 3275 (NH), 1640 cm^{-1} (C=O); nmr ($CDCl_3$) δ 6.96 (broad peak, 2 H, NH), 2.93 [s, 12 H, $N(CH_3)_2$].

Hydrazodicarboxyldipiperidide (**10**).—A solution of azodicarboxyldipiperidide (**9**, 8.32 mmol) in piperidine (50 ml, anhydrous), was refluxed until the bright yellow color of the solution was completely discharged (2 hr). The mixture was taken to dryness and the white, crystalline residue obtained was purified by crystallization (CCl_4) to give colorless needles (1.90 g, 7.84 mmol, 94%): mp 180° (lit.[19] mp 179°); ir (KBr) 3275 (NH), 1645

TABLE III

Compd	Column[16] used	Temp, °C	Flow rate, ml/min	Retention time, min
Diethylmethylamine	III	60	7	6
Methylethylamine	III	95	5	9
Diethylamine	III	95	5	12.3
N-Methylpiperidine	I	85	20	8
Piperidine	I	90	15	9
Ethylpiperidine	I	90	15	13
Piperidine	I	90	15	9
Benzylpiperidine	II	150	90	10
Piperidine	I	90	15	9
Benzaldehyde	I	115	20	9
N,N-Dimethylbenzylamine	I	125	16	12
N-Methylbenzylamine	I	115	14	16
Benzaldehyde	I	115	14	11
N,N-Diethylbenzylamine	I	120	12	37
N-Ethylbenzylamine	I	120	12	25
Benzaldehyde	I	120	12	11
Dibenzyl ether	I	185	25	10.5
Benzaldehyde	I	135	15	4
Dibenzyl thioether	I	185	25	25
Benzaldehyde	I	135	15	4

(14) G. O. Schenck and H. Formanek, *Angew. Chem.*, **70**, 505 (1958).
(15) R. C. Cookson, I. D. R. Stevens, and C. T. Watts, *Chem. Commun.*, 259 (1965).
(16) Melting points were determined on a calibrated Thomas-Hoover capillary melting point apparatus and were corrected. Ir data were recorded on a Beckmann IR-8 spectrophotometer. Nmr data were recorded on a Varian Associates Model A-60 spectrophotometer using tetramethylsilane or 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt as internal standard. Gas chromatographic data were obtained on an F & M Model 810-19, using a flame detector and columns packed with 12% w/w SE-30 (Wilkens Instrument and Research Inc.) on Chromosorb W, A. W., 60–80 mesh (Matheson Coleman and Bell) (4 ft × 0.25 in., column I), 12% Carbowax 20 M (Wilkens Instrument and Research Inc.) on Chromosorb W, A. W., 60–80 mesh (Matheson Coleman and Bell) (4 ft × 0.25 in., column II), and 40% Castorwax (Wilkens Instrument and Research, Inc.) plus 0.5% ATPEP-80 (Perkin-Elmer) on Chromosorb W, A. W. DMCS, 100–120 mesh (F & M) (10 ft × 0.125 in., column III) (Table III). Microanalyses were performed on an F & M 185 C, H, N analyzer Model 185 in this department.
(17) E. Fahr and H. Lind, *Angew. Chem., Int. Ed. Engl.*, **5**, 372 (1966).
(18) R. J. Crawford and R. Raap, *J. Org. Chem.*, **28**, 2419 (1963).
(19) W. Kesting, *Chem. Ber.*, **57**, 1321 (1924).

cm^{-1} (C=O); nmr ($CDCl_3$) δ 3.22–3.53 (m, 8 H, CH_2NCH_2), 1.38–1.70 (m, 12 H, $CCH_2CH_2CH_2C$). This compound was also obtained from 9 using the procedure outlined in the preparation of 11.

Demethylation of *N*-Methylpiperidine (Preparative Method).—To a solution of *N*-methylpiperidine (2.48 g, 25.00 mmol) in C_6H_6 (20 ml, Na dry) was slowly added a solution of 1 (6.53 g, 37.50 mmol) in C_6H_6 (20 ml, Na dry) and the mixture was refluxed for 30 min.[20] The solvent and the unreacted *N*-methylpiperidine (0.25 g, 2.52 mmol, 10%) were removed under reduced pressure and the residue was dissolved in a mixture of 4 *N* HCl (25 ml) and EtOH (10 ml). The solution was refluxed for 2 hr and taken to dryness under reduced pressure. The residue was triturated with 10 *N* NaOH solution (1 ml) and extracted with Et_2O (3 × 25 ml). The combined extracts were dried ($MgSO_4$) and distilled to give piperidine (1.3 g, 15.27 mmol, 61%).

Diethyl *N*-(Piperidinomethyl)hydrazine-*N*,*N'*-dicarboxylate Hydrochloride (12).—To a solution of *N*-methylpiperidine (0.68 g, 6.84 mmol) in C_6H_6 (25 ml, Na dry) was added 1 (2.00 g, 11.48 mmol) and the mixture was allowed to stand for 24 hr at 25°. The mixture was filtered and the clear filtrate was taken to dryness under reduced pressure. The residue was dissolved in Et_2O (20 ml, anhydrous) and to the mixture was added a saturated solution of HCl in Et_2O (15 ml, anhydrous). The white precipitate which formed was filtered and dried over P_2O_5 and NaOH pellets under vacuum for 24 hr. The solid was triturated thoroughly with Me_2CO (5 ml, anhydrous) and the undissolved portion was filtered and washed twice with Me_2CO (1 ml, anhydrous). The residue (1.30 g, 4.20 mmol, 61%) was a white, microcrystalline powder: mp 162–163° dec; ir (KBr) 3200 (NH), 1750 (C=O), 1715 cm^{-1} (C=O); nmr ($CDCl_3$) δ 4.78 (broad pea, 2 H, $^+NCH_2N$), 4.23 and 4.26 (2 q overlapping, 4 H, J = 7.5 cps, CO_2CH_2), 1.30 (t, 6 H, CCH_3).

Anal. Calcd for $C_{12}H_{24}N_3O_4Cl$: C, 46.52; H, 7.81; N, 13.56. Found: C, 46.20; H, 7.69; N, 13.30.

A solution of 12 (0.25 g, 0.87 mmol) in 4 *N* HCl (10 ml) was refluxed for 2 hr and the mixture was distilled, leaving a white residue. The formaldehyde in the distillate was determined gravimetrically as its 2,4-dinitrophenylhydrazone.[8,21] The experiment was repeated after adding a known amount of 1% formaldehyde (3.00 ml, 1.00 mmol) to the solution of 12. The concentration of formaldehyde was then estimated by comparing the results from the two experiments. After drying over P_2O_5 and NaOH pellets under vacuum, the white, crystalline residue was weighed and made into a homogeneous powder. A solution (10%) of small amount (40 mg) of the powder in CD_3OD was used for the nmr determination of piperidine hydrochloride (δ 1.80, m, 6 H, $CCH_2CH_2CH_2C$) and 6 (δ 1.22, t, 6 H, CCH_3). The overall analysis indicated that hydrolysis of 12 afforded equimolar amounts of formaldehyde, piperidine hydrochloride, and 6.

Reaction of *O*-Acetyl Bulbocapnine with Diethyl Azodicarboxylate.—*O*-Acetyl bulbocapnine (14) (0.50 g, 1.36 mmol) was dissolved in 5 ml of absolute EtOH and the solution was added slowly to diethyl azodicarboxylate (0.50 g, 2.87 mmol) under N_2. The reaction mixture was allowed to stand for 12 hr; irregular yellow crystals (0.20 g) formed, were filtered, and were washed with 0.5 ml of absolute EtOH. A second crop of crystals was obtained by evaporating the solvent under reduced pressure and washing the residue several times with ether to obtain a pale yellow, amorphous powder (0.25 g). The product (15) was recrystallized (EtOH), purified over an Al_2O_3 column (Reagent, Merck) using $CHCl_3$ as an eluent, and recrystallized [absolute EtOH–EtOAc (1:1)] to give yellow crystals (0.41 g, 0.76 mmol, 56%): mp 179–182°; ir (KBr) 3250 (NH), 1705–1750 cm^{-1} (broad band, 3 C=O); nmr ($CDCl_3$) δ 6.02 (s, OCH_2O), 4.19 and 4.20 (2 overlapping 8, 4 H, $OCCH_2$–), 3.92 (s, OCH_3), 2.71 (s, NCH_3), 2.34 (s, $OCOCH_3$). The product was analyzed immediately after purification.

Anal. Calcd for $C_{27}H_{31}N_3O_9$: C, 59.88; H, 5.77; N, 7.76. Found: C, 59.73; H, 5.59; N, 7.40.

Preparation of Substituted Benzyldialkylamines.—To a mixture of a secondary amine (55.0 mmol) and 10 *N* NaOH solution was slowly added the appropriate benzoyl chloride (37.0 mmol). The addition required 1 hr and after an additional 1 hr of stirring, 10 *N* NaOH solution (3 ml) was added. After the heat subsided, the mixture was poured into ice–H_2O and the precipitate was collected.

$LiAlH_4$ (1.6 g, 42.0 mmol) was placed in 10 ml of Et_2O, and a solution of the amide (14.0 mmol) in Et_2O was added over 1.5 hr.

After refluxing for 2–12 hr and stirring for an additional 4 hr at 25°, the excess hydride was decomposed by the slow addition of H_2O (7 ml). The mixture was stirred for 1–3 hr and filtered, and the precipitate as washed several times with Et_2O. The filtrate and washings were dried ($CaSO_4$) and the Et_2O was removed.

The product was purified by dissolving it in 2 *N* HCl and extracting the solution with C_6H_5 (3 × 25 ml). The solution was then made basic with NaOH and again extracted with C_6H_6 (3 × 50 ml). The C_6H_6 extracts were dried ($CaSO_4$) and the C_6H_6 was removed.

Reaction of *N*-Benzylpiperidine with Azodicarboxylate Esters.—A mixture of *N*-benzylpiperidine (1.20 g, 6.84 mmol) and 1 (2.00 g, 11.48 mmol) in C_6H_6 (25 ml, Na dry) was refluxed for 6 hr and filtered, and the filtrate was evaporated to dryness under reduced pressure. After drying over P_2O_5 under vacuum for 12 hr, the residue was dissolved in Et_2O (20 ml, anhydrous) and to the mixture was added a saturated solution of HCl in Et_2O (15 ml, anhydrous). The white precipitate which formed was filtered and triturated thoroughly with Me_2CO (3 ml, anhydrous). The undissolved portion was filtered and washed with Me_2CO (0.5 ml, anhydrous). The residue (1.50 g, 3.89 mmol, 57%) was a white, hydroscopic, microcrystalline powder which was very labile in the presence of moisture.

A solution of the product (50 mg) in 0.1 ml of D_2O was allowed to stand for 2 hr, after which CD_3OD (0.5 ml) was added to the mixture. Nmr analysis of the resulting clear solution indicated the presence of equimolar amounts of piperidine hydrochloride (δ 1.80, m, 6 H, $CCH_2CH_2CH_2C$), benzaldehyde (δ 9.92, s, 1 H, CHO), and 6 (δ 1.22, t, 6 H, CCH_3).

Reaction of Azodicarboxylate Esters with Tertiary Amines. General Procedure.—To a solution of the tertiary amine (5.74 mmol) in C_6H_6 (29 ml, Fisher certified reagent over Na), the azodicarboxylate ester (11.48 mmol) was added and the mixture was refluxed until no increase was observed in the quantities of secondary amines, when the mixture was analyzed by the procedure.

Determination of the Unreacted Tertiary Amines.—The reaction mixture was transferred quantitatively into a 25-ml volumetric flask and diluted to the mark with C_6H_6 (anhydrous). Aliquots (5 μl) of this solution were injected into the glc and the integration corresponding to the peak of the tertiary amine was compared to that of a standard. The standard was prepared by making 25-ml solution of the tertiary amine (5.47 mmol) in anhydrous C_6H_6. Three readings were taken in each case and their averages were compared.

Determination of the Secondary Amines.—The reaction mixture was evaporated to dryness on a rotatory evaporator and the residue was dissolved in anhydrous C_6H_6 (20 ml). Dry HCl gas was bubbled into the solution for 15 min and the solvent was removed again on a rotatory evaporator. The residue was kept in a desiccator under vacuum (0.5 mm) over NaOH for 12 hr and then extracted thoroughly with distilled H_2O (50°). The extract was transferred quantitatively into a 20-ml volumetric flask and diluted to the mark with distilled H_2O. Aliquots (5 μl) of this solution plus aliquots (5 μl) of a 20% NaOH solution were injected together into the glc. The peak corresponding to the secondary amine was compared to that obtained by injecting an equal aliquot (5 μl) of a 20% NaOH hydroxide solution. The standard was prepared by making a 20-ml solution of the HCl salt of the secondary amine in distilled H_2O. Three readings were taken in each case and their averages were compared.

Determination of Benzaldehyde.—From the previous extract, aliquots (5 μl) plus aliquots (5 μl) of distilled H_2O were injected together into the glc. The peak corresponding to benzaldehyde was compared to that obtained by injecting an equal aliquot (5 μl) of the standard together with an aliquot (5 μl) of distilled H_2O. The standard was prepared by making a 20-ml solution of benzaldehyde in a H_2O–EtOH (2:1) mixture. Three readings were taken in each case and their averages were compared.

Debenzylation of Dibenzyl Ether (Preparative Method).—A mixture of dibenzyl ether (4.96 g, 25.00 mmol) and 1 (6.53 g, 37.50 mmol) was heated at 140° for 30 min. The reaction mixture was subsequently refluxed with H_2O (30 ml) for 1 hr and extracted with C_6H_6 (3 × 50 ml). The extracts were then dried

(20) Less reactive amines required longer refluxing time.

(21) M. Mouton, *Bull. Sci. Pharmacol.*, **46**, 148 (1939); *Chem. Abstr.*, **33**, 5128 (1939).

($MgSO_4$), the solvent was removed under reduced pressure, and the residue was fractionally distilled to give benzaldehyde (2.10 g, 19.79 mmol, 79%), benzyl alcohol (2.25 g, 20.80 mmol, 83%), and unreacted dibenzyl ether (0.55 g, 2.77 mmol, 11%).

Reaction of Dibenzyl Ether with Ethyl Azodicarboxylate.—A mixture of dibenzyl ether (1.14 g, 5.74 mmol) and 1 (1.00 g, 5.74 mmol) was heated at 140° for 30 min to give a colorless solid: ir (neat) 3280 (NH), 1740 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.36 (m, 10 H, aromatic), 6.48 (s, 1 H), 4.82 (m, 2 H, $OCH_2C_6H_5$), 4.25 and 4.27 (2 q overlapping, J = 7.5 cps, 4 H, CO_2CH_2), 1.27 (t, J = 7.5 cps, 6 H, CCH_3).

A small fraction of the product (50 mg) was refluxed with H_2O (0.2 ml) for 30 min and extracted with $CDCl_3$ (2 × 0.3 ml). Nmr analysis of the combined $CDCl_3$ extracts indicated that they contained equimolar amounts of benzaldehyde (δ 9.88, s, 1 H, CHO), benzyl alcohol (δ 4.60, s, 2 H, CH_2O), and *6* (δ 1.22, t, 6 H, $CCH_2CH_2CH_2$).

Reaction of Dibenzyl Thioether with Ethyl Azodicarboxylate.—A mixture of dibenzyl thioether (1.23 g, 5.74 mmol) and 1 (1.00 g, 5.74 mmol) was heated at 140° for 30 min to give a white solid mass: ir (neat) 3280 (NH), 1740 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.25 (m, 10 H, aromatic), 6.50 (s, 1 H), 3.92 (m, 2 H, $SCH_2C_6H_5$), 4.16 and 4.17 (2 q overlapping, J = 7.5 cps, 4 H, CO_2CH_2), 1.22 (t, J = 7.5 cps, 6 H, CCH_3). A small fraction of the product (50 mg) ws refluxed under N_2 with 1 *N* HCl (0.2 ml) for 1 hr and extracted with $CDCl_3$ (2 × 0.3 ml). Nmr analysis of the combined $CDCl_3$ extracts indicated that they contained equimolar amounts of benzaldehyde (δ 9.88, s, 1 H, CHO), benzyl mercaptan (δ 3.66, s, 2 H, CH_2S), and 6 (δ 1.22, t, 6 H, $CCH_2CH_2CH_2C$).

Determination of Unreacted Dibenzyl Ether or Dibenzyl Thioether by Glc.—A known amount (2.87 mmol) of the reaction mixture between 1 and the appropriate ether was transferred quantitatively into a 25-ml volumetric flask and diluted to the mark with a 1 *N* HCl solution in a H_2O–EtOH (1:1) mixture. The mixture was analyzed against a standard of the dibenzyl ether (2.87 mmol) or the dibenzyl thioether (2.87 mmol) following the same procedure as used in the determination of tertiary amines.

Registry No.—**1**, 1972-28-7; **6**, 4114-28-7; **8**, 10465-78-8; **9**, 10465-81-3; **12**, 38910-96-2; **14**, 38910-97-3; **15**, 38910-98-4; *N*-methylpiperidine, 626-67-5; *N*-benzylpiperidine, 2905-56-8; dibenzyl ether, 103-50-4; dibenzyl thioether, 538-74-9.

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Phosphorino[4,3-*d*]pyrimidines. III. Synthesis, Resolution, and Properties of 4-Substituted Phosphorino[4,3-*d*]pyrimidines[1]

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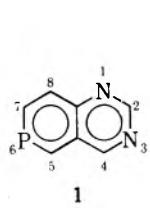
A family of 4-substituted 6-phenylphosphorino[4,3-*d*]pyrimidines has been prepared with 4-amino-1,2,5,6-tetrahydro-1-phenylphosphorin-3-carbonitrile as the key starting material. Pmr, ^{31}P nmr, infrared, and mass spectral data support the structures. Treatment of 4-amino-5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-*d*]-pyrimidine with benzyl bromide gave the corresponding phosphonium salt, which was resolved *via* its dibenzoyl tartrate salts. Ammonium bromide converted the diastereomers back to the enantiomeric bromides. Attempted methylation of 5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-*d*]pyrimidine-4-thiol gave 5,6,7,8-tetrahydro-4-(methylthio)-6-phenylphosphorino[4,3-*d*]pyrimidine 6-sulfide *without* quaternization of the phosphorus atom. Spectral data for all of these compounds are briefly discussed.

Phosphorino[4,3-*d*]pyrimidines (**1**) represent a very recent[3] and intriguing family of compounds in the area



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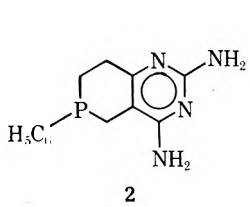

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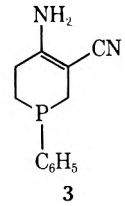

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of fused carbon–phosphorus heterocycles. The 5,6,7,8-tetrahydro derivatives are prochiral about the asymmetric phosphorus atom, and 4-substituted pyrimidines, such as adenine and 6-mercaptopurine, are well known for their biological and medicinal value.[4] Recent evidence also indicates that quinazolines substituted at the 6 position, particularly heteroatom substituents, are of potential use as antimetabolites.[5] Additionally, C–P heterocycles which possess organic functionality are extremely rare in the literature[6,7] and hence very little is known of the biological activity conveyed by the phosphorus atom. The first reported[3] phosphorinopyrimidine was the 2,4-diamino derivative **2** prepared in a direct condensation of the 2-enamine nitrile **3** with guanidine. Interestingly, recent literature[8] suggests that a method of choice for the synthesis of 4-substituted fused pyrimidines involves the utilization of 2-enamino nitriles as their triethyl orthoformate adducts.

(1) We gratefully acknowledge partial support of this work by the Public Health Service Cancer Institute, Grant CA 11967-09. This paper was presented in part at the First Rocky Mountain Regional Meeting of the American Chemical Society, Fort Collins, Colo., June 30, 1972. We are indebted to Dr. George R. Waller and Keith Kinneberg of the Biochemistry Department, Oklahoma State University, for the mass spectral data (National Science Foundation, Washington, D. C., Research Grant No. GB-20,296). We also express our thanks to the National Science Foundation (Grant No. GP 17641) for supplemental support for the purchase of the XL-100 NMR spectrometer. See *Org. Prep. Proced. Int.*, **4**, 237 (1972), for part II of this series.

(2) National Science Foundation Faculty Fellow, 1971–1972; NSF Trainee, 1970–1972; Predoctoral candidate, 1970–1972.

(3) T. E. Snider and K. D. Berlin, *Phosphorus*, **2**, 43 (1972).

(4) J. H. Lister, "Fused Pyrimidines, Part II Purines," D. J. Brown, Ed., in "The Chemistry of Heterocyclic Compounds," A. Weissberger and E. C. Taylor, Ed., Wiley-Interscience, New York, N. Y., 1971.

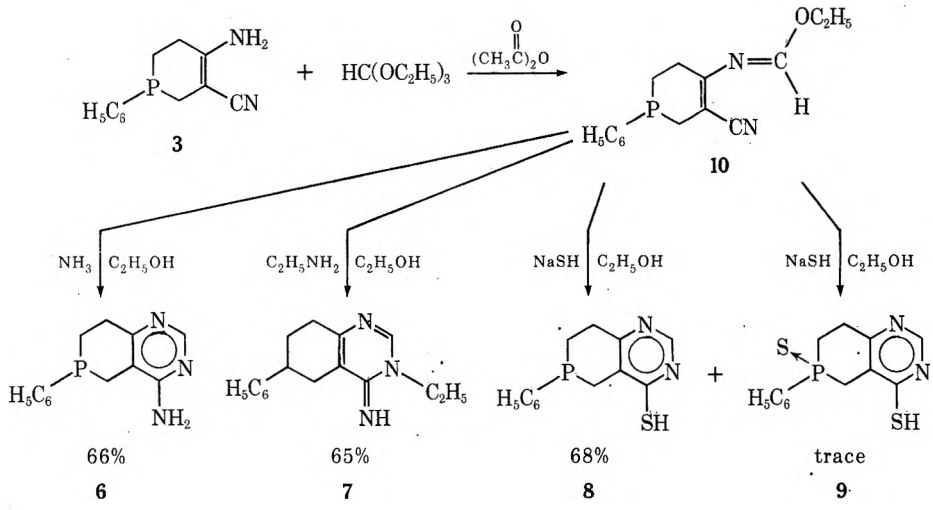
(5) J. Davoll, A. M. Johnson, H. J. Davies, O. D. Bird, J. Clarke, and E. F. Elslager, *J. Med. Chem.*, **15**, 812 (1972); E. F. Elslager, J. Clarke, L. M. Werbel, and D. F. Worth, *ibid.*, **15**, 827 (1972); J. Davoll, J. Clarke, and E. F. Elslager, *ibid.*, **15**, 837 (1972).

(6) K. D. Berlin and D. M. Hellwege, *Top. Phosphorus Chem.*, **6**, 1 (1969).

(7) T. E. Snider, C. H. Chen, and K. D. Berlin, *Phosphorus*, **1**, 81 (1971).

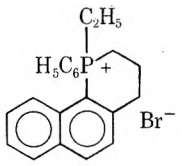
(8) E. C. Taylor, A. McKillop, and S. Vromen, *Tetrahedron*, **23**, 885 (1967); E. C. Taylor and A. McKillop, "The Chemistry of Cyclic Enaminonitriles and *o*-Aminonitriles," in "Advances in Organic Chemistry: Methods and Results," Vol. 7, E. C. Taylor, Ed., Interscience, New York, N. Y., 1970.

SCHEME I

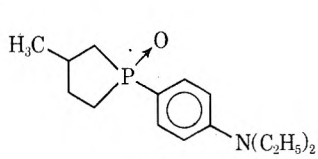


In view of the potential biological activity, novel structure, and stereochemistry of the title compounds, we elected to attempt the preparation of 4-substituted 5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-*d*]pyrimidines from 4-amino-1,2,5,6-tetrahydro-1-phenylphosphorin-3-carbonitrile (**3**).

The resolution of cyclic phosphorus compounds (and acyclic) has generally been effected by two basic methods: (a) quaternization of phosphorus to form phosphonium salts which may be resolved *via* anion exchange with reagents such as hydrogen silver L(+)- and D(−)-dibenzoyltartaric acids;[9] and (b) by blocking the phosphorus atom for reaction, generally by conversion to the phosphine oxide, and utilizing some other functionality for resolution. Thus, **4** has been resolved by Chen and Berlin[10] utilizing method a and **5** has been resolved *via* method b by Ostrogovich and Kerek[11] using camphor-13-sulfonic acid.



4



5

The synthesis of 4-substituted 6-phenylphosphorino[4,3,-*d*]pyrimidines **6**, **7**, and **8** was accomplished as outlined in Scheme I. 4-Amino-1,2,5,6-tetrahydro-1-phenylphosphorin-3-carbonitrile (**3**) was prepared according to known procedure[12] from bis(2-cyanoethyl)-phenylphosphine.[13] The ethoxymethylene derivative **10** (Scheme I), formed by boiling the 2-amino nitrile **3** in excess solution of 50:50 triethyl orthoformate and acetic anhydride, was used in crude form in reaction with either anhydrous amine (to give **6** or **7**) or anhydrous ethanolic sodium hydrosulfide (to give **8**) to effect pyrimidine formation. Derivatives such as **10** can be and have been isolated[14] but are generally used as crude material. The mechanisms involved in these transformations may be similar to those proposed by Taylor and coworkers[8,14] utilizing carbocyclic 2-enamine nitriles. It has been proposed that the yield-limiting factor in analogous reactions was the formation of the ethoxymethylene derivative.[8] The narrow range of yields (65–68%) for **6**, **7**, and **8** is additional evidence that the formation of the ethoxymethylene derivative may be the yield-limiting step in the sequence. Thus, in spite of the large size of the phosphorus atom (covalent radius 1.10 Å)[15] compared to carbon (covalent radius 0.77 Å),[15] any inherent strain in the six-membered C–P heterocycle is not sufficient to prevent formation of the fused-ring system.

The importance of acetic anhydride to the initial condensation is clearly illustrated in the synthesis of **8**. Attempted formation of **8** without the presence of acetic anhydride resulted in a yield of only 26%. With acetic anhydride, the return was increased to 66%. The function of the acetic anhydride may be to remove the ethanol converted in the reaction to ethyl acetate, which thereby helps to drive the reaction to completion. This assumes that the initial formation of **10** is an equilibrium-controlled reaction. An interesting facet in the synthesis of **8** is that a small amount of the phosphine sulfide **9** is also formed. Evidently, the phosphine is capable of abstracting sulfur from H_2S or NaSH (an apparent redox reaction). This type of exchange ($\geqslant P \rightarrow \geqslant P{=}S$) appears to be rare, although removal of sulfur by phosphorus from carbon[16,17] or phosphorus[18] is known. A possible analogous process is the formation of phosphine oxides *via* treatment of a phosphine with hydroxylamine.[19] The proposed structures of **6**, **7**, and **8** are supported by elemental analysis and their respective ir, pmr, ^{31}P nmr, and mass spectral properties.

In an ancillary experiment to confirm the structure,

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(10) C. H. Chen and K. D. Berlin, *J. Org. Chem.*, **36**, 2791 (1971).

(11) G. Ostrogovich and F. Kerek, *Angew. Chem.*, **83**, 496 (1971); *Angew. Chem., Int. Ed. Engl.*, **10**, 498 (1971).

(12) R. P. Welcher, G. A. Johnson, and V. P. Wystrach, *J. Amer. Chem. Soc.*, **82**, 4437 (1960); M. J. Gallagher and F. G. Mann, *J. Chem. Soc.*, 5110 (1962).

(13) M. N. Rauhut, I. Hechenbleikner, H. A. Currier, F. C. Schaefer, and V. P. Wystrach, *J. Amer. Chem. Soc.*, **81**, 1103 (1959); F. G. Mann and I. T. Millar, *J. Chem. Soc.*, 4453 (1952).

(14) E. C. Taylor and P. K. Loeffler, *J. Amer. Chem. Soc.*, **82**, 3147 (1960).

(15) L. A. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960, p 224.

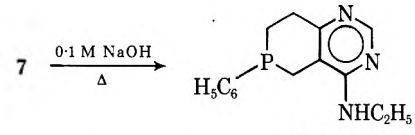
(16) E. J. Corey, *Pure Appl. Chem.*, **14**, 19 (1967).

(17) E. J. Corey and E. Block, *J. Org. Chem.*, **34**, 1233 (1969).

(18) K. D. Berlin and D. G. Hopper, *Proc. Okla. Acad. Sci.*, **46**, 85 (1966).

(19) M. D. Martz and L. D. Quin, *J. Org. Chem.*, **34**, 3195 (1969).

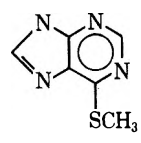
7 was rearranged to 11 by boiling the former in 0.1 *M* NaOH, known conditions for the classic Dimroth rearrangement.[20]



11

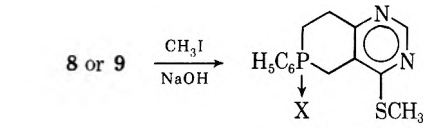
The pmr spectra of both reactant and product show anomalous features. The spectrum of 7 displays two sets of quartets of approximate equal intensity for the *N*-methylene group. Decoupling experiments (irradiating NCH_2CH_3 and observing NCH_2CH_3) reveal the collapse of the double set of quartets to a crude singlet. In an inverse decoupling experiment the observed triplet of the NCH_2CH_3 collapsed to a singlet. A third decoupling experiment (irradiation of =NH and observation of the NCH_2CH_3) showed some type of magnetic interaction, but did not cause the methylene to go to a simple quartet. Observing the spectrum in the presence of D_2O did not reveal any change in the coupling pattern. Although Brown[20] did not record any secondary splitting of this type in his discussion of the pmr spectra of *N*-methyl-4-iminoquinazolines, we have tentatively attributed this phenomenon in our system to syn–anti isomerism about the imino nitrogen and/or nonequivalence of the methylene hydrogens owing to restricted rotation. The distance between the imine hydrogen and other protons in the molecule could conceivably preclude the observation of any other splitting as a result of syn–anti isomerism. Curiously, the pmr spectrum of 11 in $DCCl_3$ shows a complete doubling of all resonance lines in an approximate intensity ratio of 3:1. A Courtauld model of 11 indicates considerable hindered rotation of the $-NHC_2H_5$ group. This steric barrier to rotation could result in conformers in which the $-NHC_2H_5$ group is syn or anti with respect to the *P*-phenyl ring. Experimental evidence supporting this explanation is: (1) the relative intensity of the doubled spectrum is solvent-dependent, and (2) the spectrum (in *o*-$C_6H_4Cl_2$) is temperature dependent with only one set of resonance signals observable at 125°.

Recent reports concerning the biological activity and potential chemotherapeutic usefulness of 6-(methylthio)purine[21] and the predicted increased water



solubility of phosphonium salts prompted us to investigate the chemistry of 6 and 8. Of particular interest were the relative reactivities of the following groups: $-\ddot{S}H$ *vs.* $C_6H_5\ddot{P}$ (alkylation *vs.* quaternization), $-\ddot{S}CH_3$ *vs.* $C_6H_5\ddot{P}$, and $-\ddot{N}H_2$ and/or pyrimidine ring N *vs.* $C_6H_5\ddot{P}$. Specifically, the question arose of competitive alkylation involving the thiol function in the presence of a phosphine without carbon–phosphorus bond formation or cleavage (in the presence of base) and whether it would be possible to quaternize a tertiary phosphine in the presence of a methylthio or nitrogen functional group.

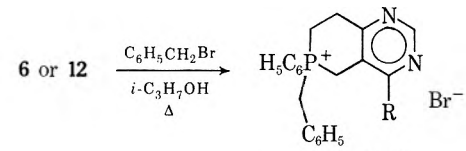
The methylation of 8 and 9 to form the methylthio derivatives 12 (89%) and 13 (71%) was accomplished



12, X = —
13, X = S

with 10% sodium hydroxide and methyl iodide. Surprisingly, derivatives 12 and 13 are volatile and are readily purified by vacuum sublimation (83–90°, 0.05 mm). Quaternization of phosphorus during the preparation of 12 was *not* observed and there was also no evidence of carbon–phosphorus bond cleavage. Hence, with respect to methylation, 8 is an exact chemical analog of aminopyrimidinethiols in which one can methylate the mercapto group in the presence of the amino function.[22]

The formation of phosphonium salts 14 and 15 from phosphines 6 and 12, respectively, indicate that



14, R = SCH_3
15, R = NH_2

the tertiary phosphine in these phosphorino[4,3-*d*]-pyrimidines is a stronger base and/or a more powerful nucleophile than the 4-methylthio or the 4-amino group. The assignment of the phosphonium structure is rigorously supported by infrared, nmr, mass spectral, and elemental analysis; except for the latter, the analyses are similar to those of the simpler precursor pyrimidines. However, most significantly, the highly positive ^{31}P nmr absorption of the phosphine precursors (*ca.* δ 44 relative to H_3PO_4; see Table I)

TABLE I
^{31}P CHEMICAL SHIFTS OF C–P HETEROCYCLES

Compd	δ	Solvent	Concn, %
3	+46.9	$HCCl_3$	5
6	+44.0	DMSO	5
7	+44.6	DMSO	5
8	+39.6	DMSO	5
11	+44.7	DMSO	5
12	+44.4	CH_3OH	5
14	−18.6	$HCCl_3$	10
15	−18.6	DMSO	10
17	−29.0	DMSO	5

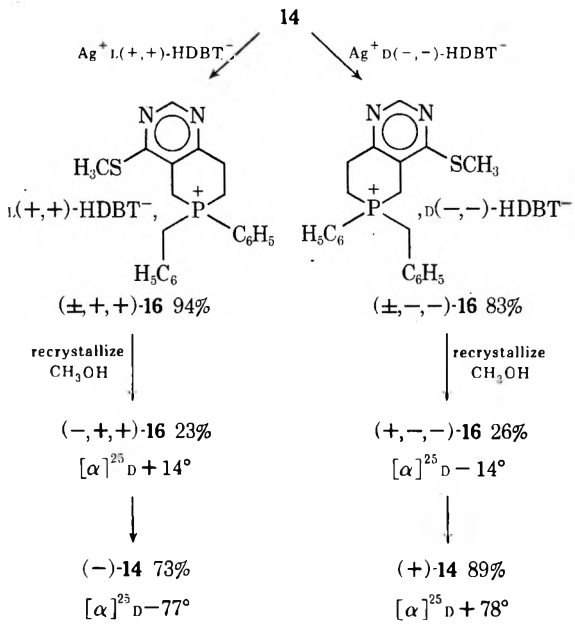
is shifted to a highly negative δ ^{31}P nmr absorption in the phosphonium salts (*ca.* δ −18; Table I). This shift from positive to negative ^{31}P absorption is characteristic of a conversion from a phosphine to a phosphonium salt and is well documented.[23] The reaction

(20) D. J. Brown and B. T. England, *Aust. J. Chem.*, **21**, 2813 (1968).
(21) J. A. Montgomery and K. Hewson, *J. Med. Chem.*, **15**, 571 (1972).
(22) D. J. Brown and S. F. Mason, "The Pyrimidines," in "The Chemistry of Heterocyclic Compounds," A. Weissberger, Ed., Interscience, New York, N. Y., 1962.
(23) M. M. Crutchfield, C. H. Dungan, J. H. Letcher, V. Mark, and J. R. Van Wazer, *Top. Phosphorus Chem.*, **5**, 1 (1967).

is complete and specific for the phosphine, as indicated by the loss of all absorption for ^{31}P at positive δ in the nmr. (Even after extended time averaging, absorption at positive δ was not observable.)

The resolution of racemic **14** was achieved by the successful isolation of the enantiomer (+)-**14** and (−)-**14**. Conversion of racemic **14** to a mixture of diastereomeric hydrogen D(−,−)-dibenzoyltartrate salts [(+,−,−)-**16** and (−,−,−)-**16**] is shown in Scheme II.

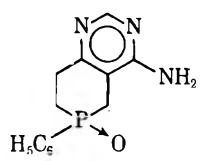
SCHEME II



Subsequent separation of (+,−,−)-**16** and (−,−,−)-**16** could be realized by repeated recrystallizations from a minimal amount of methanol.

Four recrystallizations were sufficient to purify 375 mg of (+,−,−)-**14** to a constant specific rotation, $[\alpha]^{25}D$ −14°, and a sharp melting point, 164.5–165°. The pure diastereomer (+,−,−)-**16** underwent satisfactory metathesis with ammonium bromide to form optically active (+)-**14**, $[\alpha]^{25}D$ +78° (CH_3OH), 89%, mp 250–251°. In a parallel but *separate* resolution (+)-**14** was isolated with a specific rotation of $[\alpha]^{25}D$ +77°. The equal but opposite values obtained for the specific rotations of enantiomeric **14** (Scheme II) and enantiomeric **16** [(+,−,−)-**16** and (−,+,+)-**16**], coupled with the reproducibility of the values, is strong evidence that complete resolution has been achieved.

Attempts to prepare the salt of phosphine **6** and L-mandelic acid were unfruitful. A crystalline product was not obtained even after repeated crystallization attempts. However, it is interesting that when this mixture was treated with aqueous NaOH to decompose the salt, **6** was not obtained, but instead the phosphine oxide **17** was isolated. Whether **17** is the result of simple air oxidation of **6** or was oxidized by some other material in solution is not known at this time.



17

Salts **14**–**16** have been characterized by spectral data and elemental analyses. The inclusion of solvent of crystallization, or of stoichiometric amounts of dibenzoyltartaric acid or its anions, was an anticipated difficulty which was not encountered.[10]

The predominant mass spectral fragment ions of all phosphorino[4,3-*d*]pyrimidines are listed in the Experimental Section. In general, these compounds give molecular ions of good intensity. However, phosphonium salts **14** and **15** do not show molecular ions such as Aguiar and coworkers[24] observed in certain C–P heterocycles (evaporated into the spectrometer above 300°) but instead show *m/e* M^+ − HBr as the largest major ion. The loss of HBr possibly results from electron impact within the ionizing region of the spectrometer and not from thermal decomposition on the probe. If thermal decomposition occurred, HBr would be observed in the spectrum, and it was *not* found. This situation is not true in the case of **16**, the hydrogen dibenzoyltartrate salt. Decomposition of the sample occurs in the probe at about 160°. Elimination of benzoic acid (identified by comparison with the known mass spectrum) is noted in the spectrum. The spectrum of the main sample is obtained at a probe temperature of *ca.* 200°. Benzoic acid must come from decomposition and cannot be a contaminant because benzoic acid is volatile at room temperature in the mass spectrometer.

Experimental Section

Melting points are uncorrected and were determined on a Thomas-Hoover capillary melting point apparatus in evacuated, sealed tubes. Infrared spectra were determined on a Beckman IR-5A spectrometer as potassium bromide pellets. Nuclear magnetic resonance spectra were determined on a Varian A-60 MHz high-resolution spectrometer and a Varian XL-100 MHz spectrometer. Mass spectra were determined on a LKB-9000 prototype, single-focusing magnetic sector instrument. Rotations were determined on a Rudolf Model 80 polarimeter at the sodium D line using a 2-dm cell. Elemental microanalyses were determined by Galbraith Laboratories, Knoxville, Tenn.

4-Amino-5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-*d*]pyrimidine (6).—A mixture of the 2-enamino nitrile **3**[12] (10.8 g, 0.05 mol), 80 ml (72 g, 0.49 mol) of triethyl orthoformate, and 80 ml of acetic anhydride was boiled for 1 hr. The solution of ethoxymethylene derivative **10** was concentrated to a residual oil by distillation under vacuum (70°, 0.1 mm). Anhydrous, saturated C_2H_5OH–NH_3 (200 ml, saturated at 0°) was added to the residue and the solution was stirred overnight. (After approximately 5 hr of stirring, a precipitate formed.) The mixture was filtered and the residue was washed with 25 ml of cold C_2H_5OH on the filter to yield 6.5 g, mp 194–197° of **6**. The filtrate and washings were combined and evaporated to dryness on the rotary evaporator. Trituration of the resulting oil with acetone followed by filtration gave an additional 0.8 g (mp 196–197°) of **6** for a total yield of 7.3 g (66%). Sublimation (190–200°, 0.001–0.0005 mm) gave pure **6**, mp 196–197° (lit.[3] mp 196–197°). A mixture melting point of **6** with an authentic sample showed no depression and the respective spectral properties were identical.

3-Ethyl-5,6,7,8-tetrahydro-4(3*H*)-imino-6-phenylphosphorino-[4,3-*d*]pyrimidine (7).—The crude ethoxymethylene derivative **10** was prepared as in the previous experiment. Anhydrous ethylamine (20 g) in 200 ml of absolute ethanol was added to crude **10** with stirring. After a short period of time (*ca.* 15 min), a large amount of precipitate formed. Stirring was continued overnight. The black reaction mixture was filtered, and the

(24) A. M. Aguiar, H. Aguiar, and D. Daigle, *J. Amer. Chem. Soc.*, **87**, 672 (1965).

residue was washed on the filter with two 50-ml portions of cold anhydrous ethanol to give 8.8 g (65%, dried at 78°, 1 mm) of **7** as a clean white powder. Sublimation of this sample at 135–140° (0.0001–0.0005 mm) afforded an analytical sample: mp 147–149° (s.t.); ir (KBr) 3.04, 6.14, 6.38, 7.0, 7.2 μ; pmr (DCCl$_3$) δ 1.4 (t, 3, Hz, NCH$_2$CH$_3$), 1.9–2.8 (m, 6, phosphorin ring), 4.0 (m, 2, NCH$_2$CH$_3$), 5.6 (s, broad, 1, =NH), 7.3 (m, 5, -C$_6$H$_5$), 7.65 (s, 1, 2 H); mass spectrum (70 eV) *m/e* (rel intensity) 271 (80), 242 (11), 194 (27), 181 (10), 180 (100), 162 (28), 107 (10), 28 (12). The ^{31}P magnetic resonance absorption of **7** occurred at δ +39.6 (5% in DMSO) from 85% H$_3$PO$_4$.

Anal. Calcd for C$_{15}$H$_{18}$N$_3$P: N, 15.50; P, 11.44. Found: N, 15.36; P, 11.22.

5,6,7,8-Tetrahydro-6-phenylphosphorino[4,3-*d*]pyrimidine-4-thiol (8).—A mixture of the 2-amino nitrile **3** (9.0 g, 0.0416 mol) and triethyl orthoformate (100 ml, 90 g, 0.6 mol) was boiled for 2 hr. Volatiles were then removed by distillation under reduced pressure (70°, 0.05 mm) to yield the crude ethoxymethylene derivative **10**. Sodium hydrosulfide in anhydrous C$_2$H$_5$OH (300 ml, 1.5 *N*) was added and the mixture was boiled for 12 hr. The C$_2$H$_5$OH was removed by rotary evaporation and the residual solid was dissolved in hot H$_2$O (*ca.* 150 ml). The aqueous solution was treated with decolorizing charcoal and filtered. Acidification of the hot filtrate was achieved with glacial CH$_3$CO$_2$H (H$_2$S was evolved). The precipitated product was washed with water and ethanol and dried. Two sublimations of the crude yellow product at 180–190° (0.002–0.001 mm) gave 3.1 g (26%) of analytically pure phosphine **8**: mp 230–231.5°; ir (KBr) 3.18, 3.28, 3.38, 6.24 μ; pmr (DMSO-*d*$_6$) δ 1.9–3.8 (m, 6, phosphorin ring), 2.95 (s, broad, 1, SH), 7.2 (m, 5, C$_6$H$_5$), 8.0 (s, 1, 2-H); mass spectrum (70 eV) *m/e* (rel intensity) 260 (100), 259 (18), 261 (18), 245 (17), 227 (20), 183 (21), 169 (42), 151 (16), 109 (13), 107 (11), 91 (25), 78 (12), 65 (11), 28 (11). The 40.5-MHz nmr spectrum of **8** showed ^{31}P absorption at δ +44.59 (5% in DMSO) relative to 85% H$_3$PO$_4$.

Anal. Calcd for C$_{13}$H$_{13}$N$_2$PS: N, 10.77; P, 11.92; S, 12.31. Found: N, 10.90; P, 11.80; S, 12.43.

In a second preparation, equal volumes of triethyl orthoformate and acetic anhydride were used. The yield of **8** was increased to 66% in what was otherwise an identical experiment.

4-(Ethylamino)-5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-*d*]pyrimidine (11).—A mixture of the iminopyrimidine **7** (1 g) and 50 ml of NaOH (0.1 *N*) was boiled for 1 hr. The resulting oil was separated from the water and dissolved in HCCl$_3$. The HCCl$_3$ solution was evaporated to dryness on the rotary evaporator and the residual oil was dissolved in acetone. After 2 days, during which time no crystallization occurred, the acetone solution was evaporated to dryness on the rotary evaporator to give **11** (0.7 g, 70%) as a crystalline solid. An analytical sample was obtained by sublimation at 135–140° (0.0001–0.0005 mm): mp 134–138° (s.t.); ir (KBr) 3.02, 3.4, 6.26 μ (the pmr spectrum shows two absorptions, a high-intensity and low-intensity signal, for each proton); pmr (DCCl$_3$) high intensity (low intensity) δ 1.25 (1.22) (t, 3, NHCH$_2$CH$_3$), 2.0–3.2 (m, 6, phosphorin ring), 3.25 (pentet, 2, NHCH$_2$CH$_3$), 4.8 (5.25), (s, 1, NHCH$_2$CH$_3$), 7.25 (7.3) (m, 5, C$_6$H$_5$), 8.38 (8.45) (s, 1, 2-H); mass spectrum (70 eV) *m/e* (rel intensity) 271 (100), 271 (18), 270 (13), 256 (20), 243 (15), 228 (25), 180 (16), 162 (13). The ^{31}P magnetic resonance adsorption of **11** occurred at δ +44.74 (5% in DMSO) relative to 85% H$_3$PO$_4$.

Anal. Calcd for C$_{15}$H$_{15}$N$_3$P: N, 15.50; P, 11.44. Found: N, 15.45; P, 11.18.

5,6,7,8-Tetrahydro-4-(methylthio)-6-phenylphosphorino[4,3-*d*]pyrimidine (12).—Methyl iodide (3.0 g, 0.021 mol) was added to a solution of pyrimidine **8** (5.2 g, 0.02 mol) in 35 ml of 2 *N* NaOH. The mixture was shaken vigorously and allowed to stand for 30 min while the product precipitated. The mixture was filtered, and the residue was washed (H$_2$O) while on the filter and subsequently dried under vacuum (56°, 1 mm). The crude material was then sublimed (80–90°, 0.1–0.02 mm) to yield 4.9 g (89%) of pure **12**: mp 96–98°; ir (KBr) 6.47, 6.56, 6.95, 7.06 μ; pmr (DMSO-*d*$_6$) 2.55 (s, 3, SCH$_3$), 2.1–3.2 (m, 6, phosphorin ring), 7.25 (m, 5, C$_6$H$_5$), 8.15 (s, 1, 2-H); mass spectrum (70 eV) *m/e* (rel intensity) 274 (100), 275 (27), 273 (10), 259 (27), 241 (33), 201 (11), 109 (10). The 40.5-MHz nmr spectrum of **12** showed ^{31}P absorption at δ +44.45 (5% in CH$_3$OH) relative to 85% H$_3$PO$_4$.

Anal. Calcd for C$_{14}$H$_{15}$N$_2$PS: N, 10.22; P, 11.31; S, 11.68. Found: N, 10.07; P, 11.16; S, 11.76.

5,6,7,8-Tetrahydro-4-(methylthio)-6-phenylphosphorino[4,3-*d*]pyrimidine 6-Sulfide (13).—Methyl iodide (0.79 g, 0.15 mol) was added to a solution of crude **9** (0.38 g, 0.13 mol) in 15 ml of 10% NaOH. The mixture was shaken vigorously and allowed to stand for 15 min while the product precipitated. The mixture was filtered and the residue was recrystallized (C$_2$H$_5$OH–H$_2$O). Subsequent sublimation (80–90°, 0.05 mm) of the residue gave **13**: mp 146–148° (0.28 g, 71%); ir (KBr) 6.46, 6.58, 6.98, 7.04, 7.48, 9.05 μ; pmr (DMSO-*d*$_6$) δ 2.55 (s, 3, SCH$_3$), 2.1–4.0 (m, 6, phosphorin ring), 7.6 (m, 3, *m*-C$_6$H$_5$), 7.85–8.15 (m, 2, *o*-C$_6$H$_5$), 8.8 (s, 1, 2-H); mass spectrum (70 eV) *m/e* (rel intensity) 306 (100), 308 (11), 307 (17), 305 (13), 304 (68), 291 (28), 290 (10), 273 (37), 271 (14), 260 (21), 243 (10), 165 (11), 135 (10), 109 (13), 92 (10), 91 (11), 65 (10), 63 (19).

Anal. Calcd for C$_{14}$H$_{15}$N$_2$PS$_2$: N, 9.15; P, 10.14; S, 20.92. Found: N, 9.02; P, 10.34; S, 20.76.

Preparation of 5,6,7,8-Tetrahydro-4-(methylthio)-6-benzyl-6-phenylphosphorinia[4,3-*d*]pyrimidine Bromide (14).—Benzyl bromide (1.7 g, 0.01 mol) was added to a warm solution of pyrimidine **12** (2.74 g, 0.01 mol) in 50 ml of 2-propanol. The solution was boiled for 1 hr. The solution was concentrated on the rotary evaporator to approximately 35 ml (a small amount of crystal formation was noted at this point), diluted with 100 ml of ethyl acetate, and allowed to crystallize overnight. The precipitate was filtered out and recrystallized (C$_2$H$_5$OH–ethyl acetate) to give 3.2 g (74%) of pure **14**: mp 249–251°; ir (KBr) 6.48, 7.05, 7.45, 11.51, 12.08 μ; pmr (DCCl$_3$) δ 2.45 (s, 3, SCH$_3$) 2.0–5.0 (m, 6, phosphorin ring), 5.18 and 5.45 (pair of doublets, J_{PCH} = 16.4, J_{HCH} = 3.7 Hz, -CH$_2$C$_6$H$_5$), 7.25 (s, 5, -CH$_2$C$_6$H$_5$), 7.4–7.7 (m, 3, *m*-C$_6$H$_5$), 7.7–8.0 (m, 2, *o*-C$_6$H$_5$), 8.62 (s, 1, 2-H); mass spectrum (70 eV) *m/e* (rel intensity) 364 (33), 365 (11), 363 (11), 350 (12), 349 (51), 274 (24), 273 (40), 271 (13), 121 (13), 109 (12), 92 (18), 91 (100), 82 (11), 80 (12), 65 (15). The ^{31}P nmr spectrum of **14** showed absorption at δ −18.6 (10% in CH$_3$OH) relative to 85% H$_3$PO$_4$.

Anal. Calcd for C$_{21}$H$_{22}$BrN$_2$PS: N, 6.29; P, 6.96; S, 7.19. Found: N, 6.21; P, 6.89; S, 7.16.

Preparation of 4-Amino-5,6,7,8-tetrahydro-6-benzyl-6-phenylphosphorinia[4,3-*d*]pyrimidine Bromide (15).—Benzyl bromide (0.86 g, 0.01 mol) was added to a warm solution of pyrimidine **6** (1.22 g, 0.01 mol) in 50 ml of 2-propanol and the solution was boiled for 1 hr. The solution was subsequently concentrated to *ca.* 15 ml on the rotary evaporator, diluted with 50 ml of ethyl acetate, and allowed to stand overnight. The mixture was filtered and the residue was recrystallized (C$_2$H$_5$OH–ethyl acetate) to give 1.6 g of **15** (mp 248–251°, 79%): ir (KBr) 2.94, 3.19, 3.45, 5.99, 6.15, 6.34, 6.94 μ; pmr (DMSO-*d*$_6$) δ 2.7–4.2 (m, 6, phosphorin ring), 3.6 (s, 2, NH$_2$), 4.4 (d, 2, J_{PCH} = 15.4 Hz, CH$_2$C$_6$H$_5$), 7.15 (m, 5, CH$_2$C$_6$H$_5$), 7.5–8.05 (m, 5, -C$_6$H$_5$), 8.18 (s, 1, 2-H); mass spectrum (70 eV) *m/e* (rel intensity) 333 (66), 334 (17), 332 (32), 243 (32), 242 (66), 241 (12), 166 (12), 164 (13), 134 (22), 121 (31), 109 (19), 107 (17), 92 (17), 91 (100), 82 (17), 80 (21), 65 (35), 28 (40). The ^{31}P nmr spectrum of **15** showed absorption at δ −18.6 (10% in CH$_3$OH) relative to 85% H$_3$PO$_4$.

Anal. Calcd for C$_{20}$H$_{21}$BrN$_3$P: N, 10.16; P, 7.49. Found: N, 9.76; P, 7.22.

Preparation and Resolution of (±)-5,6,7,8-Tetrahydro-4-(methylthio)-6-benzyl-6-phenylphosphorinia[4,3-*d*]pyrimidine Hydrogen D(−,−)-Dibenzoyltartrate [(±,−,−)-16].—The phosphonium salt **14** (2.225 g, mmol) dissolved in 50 ml of CH$_3$OH was slowly added to a suspension of silver hydrogen D(−,−)-dibenzoyltartrate[9] (2.79 g, 6 mmol) in boiling CH$_3$OH and the mixture was heated for 30 min. The white Ag HDBT slowly dissolved during the reaction. After *ca.* 10 min of heating, AgBr precipitated as a gray solid. The mixture was cooled and filtered to give AgBr (0.78 g, 83%) and a rose-colored, CH$_3$OH solution of **16**. The CH$_3$OH solution was concentrated on the rotary evaporator to *ca.* 20 ml, treated with 50 ml of ethyl acetate, and allowed to stand overnight. The mixture was then filtered to give 1.9 g of crude white **16**, mp 154–158°, $[\alpha]^{25}_D$ −46° (*c* 0.0100, CH$_3$OH). The filtrate was concentrated to *ca.* 20 ml, diluted with ethyl acetate, and filtered to give a second fraction of **16** as a rose-colored solid (1.0 g, mp 126–153°). Determination of the optical rotation of this fraction was not possible because of the color. The total yield was 2.9 g (83%). The first fraction was leached with boiling 2-propanol to give a residue of 1.6 g, $[\alpha]^{25}_D$ −42° (*c* 0.0100, CH$_3$OH). Three subsequent recrystallizations (CH$_3$OH) of the first fraction produced 0.4 g (23%) of material with a narrow, constant melting range (mp 154.5–165°)

and of constant specific rotation, $[\alpha]^{25}D$ −14° (c 0.0120, CH_3OH). Subsequent recrystallizations of this material failed to cause any variance in these analytical data. The direction in which the rotation had changed, *i.e.*, from negative toward positive, indicated that the diastereomer isolated was (+,−,−)-16: ir (KBr) 5.80, 6.45, 6.93, 7.33, 7.44, 7.84 μ; mass spectrum *m/e* (rel intensity) M^+ 722 absent, the spectrum of benzoic acid is observed at a probe temperature of *ca.* 160°, 391 (29), 364 (13), 349 (18), 317 (19), 290 (19), 274 (11), 273 (12), 257 (13), 109 (14), 105 (12), 92 (15), 91 (100), 77 (17), 65 (18), 51 (10), 48 (18), 47 (27), 45 (15), 44 (63), 43 (11), 28 (42).

Anal. Calcd for $C_{39}H_{35}N_2O_8PS$: C, 64.82; H, 4.84; N, 3.88; P, 4.29. Found: C, 64.75; H, 4.87; N, 3.77; P, 4.17.

In a parallel but separate experiment, 0.82 g (31%) of (+,−,−)-16 [mp 164.5–165°, $[\alpha]^{25}D$ −14° (*c* 0.0120, CH_3OH)] was obtained from 5.3 g of (±,−,−)-16 prepared as previously described.

The mother liquors of the initial recrystallizations from both experiments were combined and evaporated to dryness. The residue was recrystallized (CH_3OH) to give 3.3 g of (±,−,−)-16 enriched in the (−,−,−)-16 diastereomer, $[\alpha]^{25}D$ −84° (*c* 0.0120, CH_3OH).

Metathesis of (+)-5,6,7,8-Tetrahydro-4-(methylthio)-6-benzyl-6-phenylphosphorinia[4,3-*d*]pyrimidine Hydrogen D(−,−)-Dibenzoyltartrate [(+,−,−)-16 to the Corresponding Bromide [(+)-14].—A solution of (+,−,−)-16 (0.375 g, 0.00052 mol) and NH_4Br (0.1 g, 0.001 mol) in 25 ml of CH_3OH was boiled for 1 hr and allowed to stand overnight. The CH_3OH was evaporated on the rotary evaporator and the residue was extracted with hot $HCCl_3$ (4 × 25 ml). The $HCCl_3$ extracts were evaporated to dryness and the residue was recrystallized (CH_3OH–ethyl acetate) to give 211 mg (89%) of enantiomer (+)-14, $[\alpha]^{25}D$ +76° (*c* 0.00873, CH_3OH). Recrystallization of this sample (CH_3OH–ethyl acetate) gave 174 mg of (+)-14, mp 250–251°, $[\alpha]^{25}D$ +78° (*c* 0.00696, CH_3OH). The infrared spectrum of (+)-14 was identical with the infrared spectrum of racemic 14.

In like manner, the 0.82 g of (+,−,−)-16 from the separate but parallel resolution underwent metathesis with NH_4Br to give, after two recrystallizations (CH_3OH–ethyl acetate), 0.44 g (87%) of (+)-14, mp 250–251°, $[\alpha]^{25}D$ +77° (*c* 0.0120, CH_3OH).

Similarly, the 3.3 g, $[\alpha]^{25}D$ −84°, of residual (±,−,−)-16 enriched in (−,−,−)-16 diastereomer was subjected to metathesis with NH_4Br to give 1.9 g $[\alpha]^{25}D$ −16° (*c* 0.0120, CH_3OH), mp 249–251°, 93%, of (±)-14 enriched in (−)-14 (20% optical purity).

Preparation and Resolution of (±)-5,6,7,8-Tetrahydro-4-(methylthio)-6-benzyl-6-phenylphosphorinia[4,3-*d*]pyrimidine Hydrogen L(+,+)-Dibenzoyltartrate [(±,+,+)-16].—The levorotary enriched phosphonium bromide (±)-14, $[\alpha]^{25}D$ −16°, 1.9 g, 4.2 mmol, and silver hydrogen L(+,+)-dibenzoyltartrate[8] (2.325 g, 5 mmol) were allowed to react in the same manner utilized for the D(−,−) isomer to give 3.2 g (94%) of (−,+,+)-enriched (±,+,+)-16, mp 137–152°. Three recrystallizations of this material were sufficient to produce 433 mg (23%) of (−,+,+)-16 with a constant melting point and constant specific rotation, mp 165–166°, $[\alpha]^{25}D$ +14° (*c* 0.0120, CH_3OH).

Metathesis of (−)-5,6,7,8-Tetrahydro-4-(methylthio)-6-benzyl-6-phenylphosphorinia[4,3-*d*]pyrimidine Hydrogen L(+,+)-Dibenzoyltartrate [(−,+,+)-16] to the Corresponding Bromide [(−)-14].—Utilizing the procedure previously described for metathesis, 433 mg (0.6 mmol) of (−,+,+)-16 and 0.2 g (2 mmol) of NH_4Br reacted to give, after two recrystallizations, (−)-14, 194 mg (73%), mp 250–251°, $[\alpha]^{25}D$ −77° (*c* 0.0120, CH_3OH). The infrared spectrum of (−)-14 was identical with the infrared spectrum of racemic 14.

Preparation of 4-Amino-5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-*d*]pyrimidine 6-Oxide (17).—Phosphorinopyrimidine 6 (2.43 g, 0.01 mol) in 25 ml of C_2H_5OH and a solution of D(−)-mandelic acid (1.52 g, 0.01 mol) in 25 ml of C_2H_5OH were mixed and the solution was boiled for 1 hr. The solvent was subsequently evaporated and the resulting oil was submitted to recrystallization attempts utilizing a variety of solvents. After *ca.* 8 weeks, crystallization had not occurred. Hence, the solvents were removed *via* rotary evaporator and the resulting oil was treated with 200 ml of 10% NaOH to decompose any salt present and to remove the mandelic acid. The reaction mixture was filtered to give a light brown powder. Recrystallization of this powder, with the aid of Nuchar, from C_2H_5OH–H_2O, gave 1.9 g of 17 as white crystals: mp 294–296°; 73%; ir (KBr) 3.02, 3.18, 6.03, 6.34, 6.40, 6.49, 6.75, 6.88 μ; pmr (DMSO-d_6) δ 2.0–3.3 (m, 6, phosphorin ring), 6.72 (s, 2, NH_2), 7.56 (m, 3, *m*- and *p*-PC_6H_5), 7.64–7.88 (m, 2, *o*-PC_6H_5), 8.18 (s, 1, 2-H); mass spectrum (70 eV) *m/e* (rel intensity) 259 (100), 260 (17), 258 (21), 182 (21), 135 (21), 134 (56), 107 (14), 54 (10), 47 (19). The 40.5-MHz nmr spectrum of 17 showed ^{31}P absorption at δ −29.0 (5% in DMSO) relative to 85% H_3PO_4.

Anal. Calcd for $C_{13}H_{14}N_3OP$: N, 16.22; P, 11.97. Found: N, 16.11; P, 11.84.

Registry No.—**3,** 23848-09-1; **6,** 38626-62-9; **7,** 38626-63-0; **8,** 38626-64-1; **9,** 38626-65-2; **10,** 38626-66-3; **11,** 38626-67-4; **12,** 38626-68-5; **13,** 38626-69-6; (±)-**14,** 38626-70-9; (+)-**14,** 38626-71-0; (−)-**14,** 38626-72-1; **15,** 38626-73-2; (±,−,−)-**16,** 38626-74-3; (+,−,−)-**16,** 38626-75-4; (−,−,−)-**16,** 38626-76-5; (±,+,+)-**16,** 38677-76-8; (−,+,+)-**16,** 38677-77-9; (+,+,+)-**16,** 38626-77-6; **17,** 38626-78-7; triethyl orthoformate, 122-51-0; silver hydrogen, D(−,−)-dibenzoyltartrate, 38823-92-6; silver hydrogen L(+,+)-dibenzoyltartrate, 38823-93-7; D(−)-mandelic acid, 611-71-2.

Reactions of the Nitrosonium Ion. V. Nitrosative Cleavage of the Carbon–Nitrogen Double Bond. The Attempted Exchange of Oxygen for Nitrogen[1a]

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N-Benzylidenetriphenylmethylamine reacts with $NO^+BF_4^-$ to give benzaldehyde, nitrogen, and the triphenylmethyl cation. When *N*-benzylidenebenzhydrylamine is similarly treated with $NO^+BF_4^-$ in acetonitrile, nitrogen, nitric oxide, and nitrous oxide are formed; and when the reaction solution is quenched with water, benzaldehyde, benzophenone, protonated imine, and *N*-(diphenylmethyl)acetamide are observed. With *N*-benzylidenebenzylamine, silane quenching of the reaction products gives dibenzyl ether; using *N*-benzylidenebenzylamine-α-d_2, the dibenzyl ether formed contains only two deuterium atoms per molecule. Similar reactions with other imines, pyridines, and various unsaturated heterocyclic compounds are presented. Results are discussed in terms of competitive nitrosative cleavage of the carbon–nitrogen double bond and hydrogen transfer to the nitrosyl group.

We have previously reported that *N*-benzylideneanilines react with nitrosonium salts under mild conditions in anhydrous media to produce benzaldehydes and benzenediazonium salts (eq 1).[2] Yields were generally greater than 90%, and no major competing side reactions were observed. Similar results had been reported for the reactions of benzylideneaniline with nitrosyl chloride, dinitrogen tetroxide, and nitrosylsulfuric acid.[3]

$$ArCH{=}NAr' + NO^+X^- \longrightarrow ArCHO + Ar'N_2^+X^- \quad (1)$$

Although no previous study has been reported, we expected that *N*-alkylimines would also undergo nitrosative cleavage of the carbon–nitrogen double bond to form a carbonyl compound and, following the loss of nitrogen, an alkyl cation (Scheme I). If the carbonyl compound produced is the most basic species in solution, O-alkylation by the carbenium ion would provide the net result of an oxygen exchange for the imine nitrogen (eq 5). For this purpose nitrosonium salts, such as $NO^+BF_4^-$, are most suitable since the nonbasic anion is not expected to undergo reactions with carbenium ion products.[4]

SCHEME I

$$R_2C{=}NR' + NO^+ \longrightarrow R_2C{=}O + R'N_2^+ \quad (2)$$

$$R'N_2^+ \longrightarrow R'^+ + N_2 \quad (3)$$

$$R'^+ + R_2C{=}O \longrightarrow R_2C{=}\overset{+}{O}{-}R' \quad (4)$$

$$R_2C{=}NR' + NO^+ \longrightarrow R_2C{=}\overset{+}{O}R' + N_2 \quad (5)$$

Results

***N*-Benzylidenetriphenylmethylamine.**—To determine if nitrosative cleavage would occur with *N*-alkylimines to produce carbonyl compounds, nitrogen, and alkyl cations, *N*-benzylidenetriphenylmethylamine was treated with an equivalent amount of nitrosonium tetrafluoroborate in acetonitrile to give the results shown in eq 6. The benzylideneimines were chosen because side reactions with the benzylidene moiety do not occur and because benzaldehyde is stable toward $NO^+BF_4^-$ under the reaction conditions studied.[2] A nearly quantitative yield of nitrogen was observed. The pmr spectrum of the reaction solution after complete nitrogen evolution was identical with that produced when an equimolar amount of benzaldehyde and trityl salt were added to acetonitrile. Benzaldehyde, produced in greater than 95% yield, was confirmed prior to quenching and work-up by glpc analysis. Addition of triethylsilane, an effective trapping agent for carbenium ions,[5] yielded triphenylmethane quantitatively; quenching with water gave triphenylmethanol. The protonated imine was produced when small amounts of water were present in the reaction medium.

$$C_6H_5CH{=}NC(C_6H_5)_3 + NO^+BF_4^- \xrightarrow[25°]{CH_3CN} C_6H_5CHO + N_2 + (C_6H_5)_3C^+BF_4^- \quad (6)$$

***N*-Benzylidenebenzhydrylamine** was similarly treated with $NO^+BF_4^-$ (1.1 equiv) in anhydrous acetonitrile at room temperature (eq 7). In addition to nitrogen, nitric oxide and a small amount of nitrous oxide were produced; the total yield of gaseous products, based on the expected production of 1 mol of gas per mole of imine, was greater than 70%. Benzaldehyde and benzophenone were observed by pmr spectroscopy and from glpc analysis prior to quenching; protonated *N*-benzylidenebenzhydrylamine accounted for approximately 60% of the reaction products. Quenching the reaction mixture with 1 equiv of water produced *N*-(diphenylmethyl)acetamide (16–26%); the same yields of benzaldehyde, benzophenone, and protonated imine were observed before and after quenching. The *N*-benzhydrylacetonitrilium ion could not be detected in the reaction solution prior to

$$C_6H_5CH{=}NCH(C_6H_5)_2 \xrightarrow[CH_3CN,\ 25°]{NO^+BF_4^-} \underset{33\%}{C_6H_5CHO} + \underset{15\%}{(C_6H_5)_2C{=}O} + \underset{57\text{–}67\%}{C_6H_5CH{=}\overset{+}{N}(H)CH(C_6H_5)_2} + N_2 + NO + N_2O \quad (7)$$

(1) (a) These results were presented in part at the 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 28 to April 2, 1971, Abstracts, ORGN 15; (b) National Science Foundation Undergraduate Research Participant, summer, 1971; (c) National Science Foundation Undergraduate Research Participant, summer, 1969.

(2) M. P. Doyle, W. Wierenga, and M. A. Zaleta, *J. Org. Chem.*, **37**, 1597 (1972).

(3) (a) J. Turcan, *Bull. Soc. Chim. Fr.*, **2**, 627 (1935); (b) R. M. Scribner, *J. Org. Chem.*, **29**, 3429 (1964).

(4) M. P. Doyle and W. Wierenga, *J. Amer. Chem. Soc.*, **94**, 3901 (1972).

(5) F. A. Carey and H. S. Tremper, *J. Org. Chem.*, **36**, 758 (1971), and references cited therein.

quenching.[6] Quenching with triethylsilane yielded diphenylmethane, presumably produced from both the benzhydryl cation and benzophenone.[4,7]

When the nitrosation of *N*-benzylidenebenzhydrylamine by $NO^+BF_4^-$ was run in chloroform-d_1 at 25°, a 54% yield of gaseous products was obtained in addition to benzaldehyde (42%) and the protonated imine (44%). After quenching with water (1.2 equiv), benzaldehyde (44%), benzophenone (15%), and protonated imine (47%) were the only components of the mixture that could be identified; no benzhydrol was detected. In a separate experiment, triethylsilane quenching (2 equiv) yielded diphenylmethane in 52% yield along with 40% of protonated *N*-benzylidenebenzhydrylamine and 15% of dibenzyl ether. When the imine–$NO^+BF_4^-$ reaction was carried out in chloroform-d_1 at 65°, the products and per cent yields were similar to those obtained at 25° with the exception that diphenylmethane (5%) was produced prior to quenching.

Although *N*-benzylidenebenzhydrylamine undergoes nitrosative cleavage with nitrosonium salts, competing reactions that lead to benzophenone, diphenylmethane, nitric oxide, and nitrous oxide are also evident. No evidence was obtained for the production of O-alkylated benzaldehyde using this imine.

***N*-Benzylidenebenzylamine.**—The addition of *N*-benzylidenebenzylamine to an equivalent amount of $NO^+BF_4^-$ in anhydrous acetonitrile at 25° yielded gaseous products (54%), benzaldehyde, and the corresponding N-protonated imine (54%). The protonated imine showed no tendency to react with $NO^+BF_4^-$ even when the salt was used in large excess or when the reaction was run at temperatures as high as 60°.

The yield of benzaldehyde from the reaction in acetonitrile was 28% by pmr spectroscopy, based on integration of the characteristic signal at δ 10.0 and compared to an internal standard. This yield, however, would not reflect the total yield of benzaldehyde from nitrosative cleavage if the process given in eq 4 had occurred. In separate experiments between 0.5 and 1.0 equiv of benzaldehyde was added to an acetonitrile solution of the *N*-benzylacetonitrilium ion, prepared from the reaction between benzyl azide and nitrosonium tetrafluoroborate.[6] The pmr signals of both benzaldehyde (δ 10.0) and the *N*-benzylacetonitrilium ion (δ 5.37 and 2.85) were diminished; as the amount of benzaldehyde was increased, the integrated signal of benzaldehyde also increased while those for the nitrilium ion decreased. However, both species could be observed even at 0.5 and 1.0 equiv of added benzaldehyde; only when an excess of benzaldehyde (1.5 equiv) was added were the nitrilium ion signals absent. No absorptions other than those of benzaldehyde and the *N*-benzylacetonitrilium ion were evident under our pmr conditions (37°, 0.4 *M* nitrilium ion).

Although we were not able to detect O-alkylated benzaldehyde, similar compounds have been observed in other media.[8] The observation of benzaldehyde and the nitrilium ion, even when equivalent amounts of both compounds were present in solution, suggests an equilibrium process (eq 8). Addition of triethylsilane

$$C_6H_5CH_2\overset{+}{N}{\equiv}CCH_3 + C_6H_5CHO \rightleftharpoons \underset{\text{I}}{[C_6H_5CH{=}\overset{+}{O}CH_2C_6H_5]} + CH_3CN \quad (8)$$

produced dibenzyl ether, the expected reduction product from I.[7]

Addition of 10 equiv of water to the acetonitrile solution from the reaction of *N*-benzylidenebenzylamine with $NO^+BF_4^-$ gave benzaldehyde (95%), benzylamine (55%), *N*-benzylacetamide (25%), and benzyl alcohol (10%). No significant differences in the identities or yields of products were observed when the reaction was performed at −13° or when $NO^+BF_4^-$ was added to *N*-benzylidenebenzylamine.

The addition of triethylsilane (1.2 equiv) to the acetonitrile reaction solution after complete gas evolution gave dibenzyl ether (6%). No benzaldehyde was observed by pmr spectroscopy immediately following the addition of triethylsilane. The yield of protonated imine was not noticeably affected by silane quenching.

In acidic media benzaldehyde is reduced by trialkylsilanes to dibenzyl ether in high yield.[9] This explains the formation of dibenzyl ether from silane quenching of the products from the reaction between *N*-benzylidenebenzhydrylamine and NO^+BF_4 in chloroform-d_1, noted earlier. Thus, the presence of dibenzyl ether from silane quenching in the nitrosative cleavage reactions of *N*-benzylidenebenzylamine does not unambiguously suggest the process described in Scheme I. We, therefore, treated *N*-benzylidenebenzylamine-α-d_2 with $NO^+BF_4^-$ in anhydrous acetonitrile at 25°. The yields of gaseous products, protonated imine, and observed benzaldehyde were identical with those from the same reaction with the undeuterated compound. Quenching with triethylsilane followed by addition of water and work-up yielded dibenzyl ether-α-d_2 (II), strongly suggesting the process shown in eq 9. A 5% yield of II was obtained.

$$C_6H_5CH{=}NCD_2C_6H_5 \xrightarrow[CH_3CN]{NO^+BF_4^-} C_6H_5CH{=}\overset{+}{O}CD_2C_6H_5 \xrightarrow{Et_3SiH} \underset{\text{II}}{C_6H_5CH_2OCD_2C_6H_5} \quad (9)$$

Treatment of *N*-benzylidenebenzylamine with $NO^+BF_4^-$ in chloroform at 55° gave gaseous products (65%), benzaldehyde (30%), and the protonated imine (30%) as the only products definable by pmr spectroscopy. The pmr spectrum did, however, exhibit a distinct signal at δ 3.95, characteristic of a ring-substituted diphenylmethane (>5%); no attempt was made to characterize this product. Under similar reaction conditions the benzyl cation, produced from the reaction between benzyl azide and $NO^+BF_4^-$, undergoes Friedel–Crafts alkylation of benzene.[10] The addition of 2 equiv of triethylsilane followed by addition of water and work-up gave an 18% yield of dibenzyl ether with 55 mol % of recovered benzaldehyde. In separate experiments the addition of tri-*n*-butylsilane and triphenylsilane gave dibenzyl ether in 10 and 11% yield,

(6) The *N*-alkylacetonitrilium ions, produced in high yields from alkyl azides and nitrosonium salts, have been detected under similar reaction conditions: M. P. Doyle and W. Wierenga, *J. Amer. Chem. Soc.*, **94**, 3869 (1972).

(7) M. P. Doyle, D. J. DeBruyn, and D. A. Kooistra, *ibid.*, **94**, 3896 (1972).

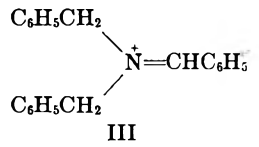
(8) G. A. Olah and J. M. Bollinger, *ibid.*, **89**, 2993 (1967).

(9) D. N. Kursanov, A. N. Parnes, N. M. Loim, and G. V. Bakalova, *Proc. Acad. Sci. USSR*, **179**, 328 (1968).

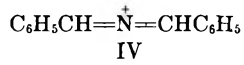
(10) Unreported results from our laboratory.

respectively. Quenching with sodium borohydride gave only a small amount (<2%) of dibenzyl ether.

An attempt was made to trap reaction products, such as I, by the addition of cyanide salts following complete gas evolution from the reaction between *N*-benzylidenebenzylamine and $NO^+BF_4^-$ in acetonitrile. The same procedure was used that had been successful in trapping compound III in experiments described by



III



IV

Smith and Loeppky.[11] Under our reaction conditions no evidence for cyanide products derived from I, III, or IV was obtained, and no phenylacetonitrile was produced.

Since the major competing processes in the nitrosative cleavage of imines are those leading to protonated imines, we attempted to treat the imine with $NO^+BF_4^-$ in the presence of a base that was stable toward $NO^+BF_4^-$, yet sufficiently strong to accept the protons produced in these reactions. Pyridine was chosen because Olah has reported that nitrosonium salts react with pyridine to form stable N-nitrosated pyridinium salts.[12] Addition of equimolar amounts of *N*-benzylidenebenzylamine and pyridine to $NO^+BF_4^-$ in acetonitrile at 29° gave, however, only 18% of gaseous products and no improvement in the yields of products from the nitrosative cleavage reaction.

Other Imines.—When *N*-benzylidene-*tert*-butylamine was added to an equivalent amount of $NO^+BF_4^-$ in anhydrous acetonitrile at 29°, a 76% yield of gaseous products, 73% of the corresponding protonated imine, and 17% of benzaldehyde were obtained; after quenching with water and work-up a minor amount (<5%) of *N*-*tert*-butylacetamide was observed. *N*-Benzylidenemethylamine was similarly treated with $NO^+BF_4^-$ to give gaseous products (45%), protonated imine (49%), and benzaldehyde (23%); addition of triethylsilane to the reaction solution after complete gas evolution did not produce benzyl methyl ether.

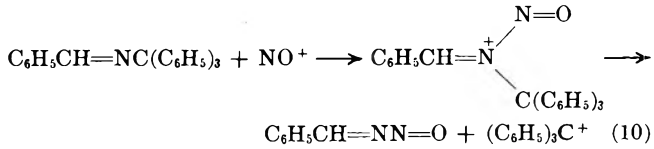
Pyridines.—Results from the reaction of *N*-benzylidenebenzylamine with $NO^+BF_4^-$ which indicated the production of I prompted us to consider the possibility that pyridine could also undergo nitrosative cleavage with an exchange of oxygen for nitrogen. Although pyrylium salts can be converted to pyridines, no method exists for the direct preparation of pyrylium compounds from pyridines.[13] Since both 2,4,6-trimethyl- and 2,4,6-triphenylpyrylium tetrafluoroborates are stable compounds and easily characterized, the corresponding trisubstituted pyridines were chosen for study.

Results similar to those reported by Olah[12] were obtained when pyridine was added to an excess of $NO^+BF_4^-$. When 2,4,6-trimethylpyridine was added to a slight molar excess of $NO^+BF_4^-$ in anhydrous acetonitrile, approximately 16 mol % of gaseous products, identified as mainly nitrous oxide and nitrogen dioxide, was produced. Only 2,4,6-trimethylpyridinium tetrafluoroborate (>90%) was observed by pmr and ir analyses. Similarly, 2,4,6-triphenylpyridine produced only the corresponding pyridinium salt when added to $NO^+BF_4^-$ in acetonitrile; again, a low yield (<20%) of gaseous products was obtained. Under the same reaction conditions, 2,4,6-trimethylpyrylium tetrafluoroborate was unaffected by $NO^+BF_4^-$. When 2,4,6-trimethylpyridine was added to 0.5 equiv of $NO^+BF_4^-$ in acetonitrile at room temperature, the same yield of gaseous products was obtained (16% based on the pyridine, 32% based on $NO^+BF_4^-$) and only the pyridinium salt (50%) and unreacted pyridine (50%) were observed; addition of another 0.5 equiv of $NO^+BF_4^-$ to the reaction solution increased the yield of pyridinium salt to 100%. Neither changing the rate of addition of the pyridine, nor increasing the reaction temperature to 60°, nor using as much as a tenfold excess of $NO^+BF_4^-$, nor changing the reaction solvent from acetonitrile to nitromethane or to using no solvent, nor performing the reaction under a dry nitrogen atmosphere, changed the course of the reaction. No evidence was obtained for the production of pyrylium salts.

Other Heterocyclic Compounds.—Similar attempts were made to exchange oxygen for nitrogen in imidazole, *N*-methyl-, and *N*-benzylimidazole, 2,5-diphenyloxazole, benzoxazole, benzothiazole, phenazine, and 1*H*-1,2,4-triazole. Gaseous products, mainly nitrogen dioxide, and the protonated substrate were produced. Again, no evidence for an exchange of oxygen for nitrogen was obtained.

Discussion

Results from the reaction of *N*-benzylidenetriphenylmethylamine with $NO^+BF_4^-$ demonstrate that nitrosative cleavage of *N*-alkylimines does occur with formation of a carbonyl compound, nitrogen, and a carbenium ion. In this case, however, an alternate mechanism to that given in Scheme I, involving N-nitrosation followed by dissociation to the trityl cation and *N*-nitrosobenzylideneimine (eq 10), cannot be excluded; *N*-nitrosobenzylideneimine would be expected to yield nitrogen and benzaldehyde in a manner analogous to that of *N*-nitrosoketimines.[2,14] With *N*-alkylimines able to provide less stable carbenium ions, nitrosative cleavage is also observed; and the occurrence of a similar dissociation of an initially formed N-nitrosated *N*-alkylimine is less likely.



$$C_6H_5CH{=}NN{=}O + (C_6H_5)_3C^+ \quad (10)$$

With *N*-benzylidenebenzylamine, nitrosative cleavage with loss of nitrogen results in the production of the O-alkylated benzaldehyde, I. The existence of this species, which represents a net exchange of oxygen for nitrogen in the nitrosative cleavage reaction, rests mainly on the results of silane quenching of the products from the reaction of *N*-benzylidenebenzylamine-α-d_2 with $NO^+BF_4^-$. The observation of dibenzyl

(11) P. A. S. Smith and R. N. Loeppky, *J. Amer. Chem. Soc.*, **89**, 1147 (1967).

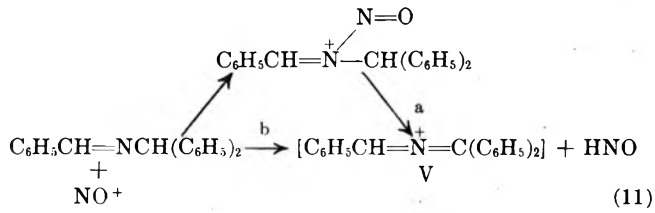
(12) G. A. Olah, J. A. Olah, and N. A. Overchuk, *J. Org. Chem.*, **30**, 3373 (1965).

(13) A. T. Balaban, W. Schroth, and G. Fischer, *Advan. Heterocycl. Chem.*, **10**, 241 (1969).

(14) (a) C. J. Thoman and I. M. Hunsberger, *J. Org. Chem.*, **33**, 2852 (1968); (b) J. Jappy and P. N. Preston, *Tetrahedron Lett.*, 1157 (1970).

ether having two deuterium atoms per molecule can only be explained by reduction of an O-alkylated benzaldehyde; the reduction of benzaldehyde alone would have resulted in dibenzyl ether with no deuterium per molecule. The yield of dibenzyl ether from reactions in acetonitrile is low, accounting for less than 15% of the reacted *N*-benzylidenebenzylamine. Since benzaldehyde is observed in relatively high yield (>50% of reacted imine) and not observed following triethylsilane quenching, reduction products other than dibenzyl ether, which were not identified in this present study, must account for the difference. Neither the protonated imine nor the *N*-benzylacetonitrilium ion lead to dibenzyl ether; the protonated imine is unaffected by silane quenching, and the *N*-benzylacetonitrilium ion is reduced to the corresponding imine.

The production of benzophenone from *N*-benzylidenebenzhydrylamine can be explained by hydrogen transfer to the nitrosyl group (eq 11a) in an elimination



(11)

reaction similar to that observed by Smith and Loeppky in the nitrosative cleavage of tertiary amines.[11] Alternatively, hydride abstraction from the imine by the nitrosonium ion (eq 11b), analogous to that observed by Olah and Friedman with cumene,[15] would also explain the observed results. Nitrosyl hydride is known to form nitrous oxide and water (eq 12)[11,16] and, when

$$2HNO \longrightarrow N_2O + H_2O \quad (12)$$

produced in the presence of the nitrosonium ion, nitric oxide and a proton (eq 13);[11,17] both nitrous and nitric

$$HNO + NO^+ \longrightarrow 2NO + H^+ \quad (13)$$

oxides were observed as gaseous products from the reaction of *N*-benzylidenebenzhydrylamine with $NO^+BF_4^-$. Although no evidence for the independent existence of V was obtained, the production of benzophenone, nitrous oxide, and nitric oxide requires that hydrogen transfer must have occurred. Under the same reaction conditions the solvent does not react with $NO^+BF_4^-$, and no evidence for isomerization of *N*-benzylidenebenzhydrylamine to *N*-benzhydrylidenebenzylamine was obtained. The production of diphenylmethane when the nitrosative cleavage reaction was run in chloroform at elevated temperatures indicated that hydride abstraction by the benzhydryl cation might also yield V; however, attempts to generate V using trityl salts in acetonitrile at 65° were unsuccessful.

The decomposition of nitrosyl hydride also partially explains the formation of protonated imines in these reactions. However, if the protonated imine is produced only through the hydrogen transfer reaction that leads to benzophenone (eq 11), only a 15% yield of protonated imine would have been expected. The high yields of protonated imine, produced under reaction conditions where water contamination was carefully avoided, require other reaction processes. Since we are able to account for greater than 90% of the reaction products in most reactions, only a small proportion of *N*-alkylimine must be involved in other proton-producing processes. This latter explanation also accounts for the sole production of pyridinium salts in the reactions of trisubstituted pyridines with $NO^+BF_4^-$; if nitrosative cleavage of the carbon–nitrogen bond is involved, the unsaturated ring-opened product might be expected to be quite susceptible to electrophilic attack by the nitrosonium ion, followed by elimination of a proton.

The results obtained in this study can be explained by nitrosative cleavage of the carbon–nitrogen double bond in competition with hydrogen transfer to the nitrosyl group. Alternate processes that lead to protonation of the substrate utilize only a small fraction of the total amount of substrate; however, protonation of the substrate quenches further reaction with nitrosonium salts.

Experimental Section

General.—Instrumentation has been described.[6] Gaseous products were identified by mass spectroscopy using a Finnigan Model 1015 mass spectrometer at 70 eV, as well as by infrared analyses with a Perkin-Elmer Model 621 spectrometer. Use was made of 5-ft columns of 20% SE-30 on Chromosorb P and 3% SE-30 on Varaport 30 and of 3-ft columns of 20% Carbowax 20M on Chromosorb P. Nitrosonium salts were obtained from Ozark Mahoning Co. and were dried over phosphorus pentoxide in a vacuum desiccator at 1.0 Torr prior to use. Analytical grade acetonitrile and nitromethane were distilled twice from calcium hydride and stored over molecular sieves. The water content of the acetonitrile was determined by measuring the amount of *N*-benzylacetamide formed in the reaction between benzyl azide and $NO^+BF_4^-$;[6] analysis of the reaction products by pmr spectroscopy shows *N*-benzylacetamide when water is present. The amide is formed quantitatively from the reaction of water with an equivalent amount of the *N*-benzylacetonitrilium ion, and coexists in acetonitrile solutions with the acetonitrilium ion; the acetonitrile generally contained less than 0.02 mmol of water per ml. Chloroform was purified by standard procedures; chloroform-d_1 was obtained from Merck Sharpe and Dohme and used without further purification.

***N*-Benzylidenealkylamines.**—*N*-Benzylidenetriphenylmethylamine was prepared from benzaldehyde and triphenylmethylamine in refluxing benzene by removal of water with a Dean–Stark trap. The crude product was recrystallized from chloroform–ether, yielding white crystals in 83% yield: mp 152.0–152.5°; pmr ($CDCl_3$) δ 7.87 (s, 1, CH=N), 7.9–7.7 (m, 2, *o*-H), 7.6–7.1 (m, 18, Ph).

Anal. Calcd for $C_{26}H_{21}N$: C, 89.88; H, 6.09. Found: C, 89.90; H, 6.16.

N-Benzylidenebenzhydrylamine,[18] *N*-benzylidenebenzylamine,[19] and *N*-benzylidene-*tert*-butylamine[20] were prepared by the same method and purified by recrystallization or distillation. *N*-Benzylidenemethylamine was commercially available.

General Procedure for Nitrosation of Imines.—The *N*-alkylimine (5.0 mmol) in 7 ml of anhydrous acetonitrile or chloroform was added dropwise to a constantly stirred solution of $NO^+BF_4^-$ (5.5 mmol) in 3 ml of the same solvent. Reactions were run in a three-necked flask fitted with a dropping funnel, thermometer, and gas outlet tube. *N*-Benzylidenetriphenylmethylamine was added as a solid in portions from an erlenmeyer flask fitted to the reaction flask with tygon tubing. Except when mass spectral identification of the gaseous products was made, the entire system was flushed with dry nitrogen prior to addition. The imine was added at such a rate (15–30 min) as to cause no sig-

(15) G. A. Olah and N. Friedman, *J. Amer. Chem. Soc.*, **88**, 5330 (1966).
(16) F. Q. Kohant and F. W. Lamps, *ibid.*, **87**, 5795 (1965).
(17) E. J. Strojny, R. T. Iwamasa, and L. K. Frevel, *ibid.*, **93**, 1171 (1971).
(18) A. Lespagnol, S. Dicop, and J. Vanlerenberghe, *Bull. Soc. Pharm. Lille*, 49 (1945).
(19) G. Mignonac, *Ann. Chim. (Paris)*, [11], **2**, 225 (1934).
(20) E. Cordes and W. Jencks, *J. Amer. Chem. Soc.*, **85**, 2843 (1963).

nificant rise in the reaction temperature. Temperature control was effected by using an appropriate heating or cooling bath. For reactions run with pyridine, an equimolar amount of pyridine was added to $NO^+BF_4^-$ prior to the imine.

Total gas evolution was measured on the closed system by water displacement from a calibrated gas buret. Gas evolution was usually complete within 1 hr after addition at room temperature. The yield of gaseous products was calculated on the basis of 1 mol of gas per mole of imine. Gaseous products from the reactions of $NO^+BF_4^-$ with *N*-benzylidenetriphenylmethylamine and -benzhydrylamine were identified by mass spectroscopy using representative gas samples.

A pmr spectrum of the reaction products was usually obtained prior to quenching. Glpc analyses were also used at this point to detect products prior to quenching. Following analysis between 2 and 10 equiv of water or deuterium oxide was added, usually within 30 min after gas evolution was complete; and a pmr spectrum of the reaction solution was again obtained. For reactions in which silanes were used as the quenching agent, between 1 and 2 equiv of the appropriate silane was added instead of water. Methylene chloride (25 ml) was added along with water (20 ml) and the resulting layers were separated after thorough mixing. The aqueous layer was washed once with methylene chloride (25 ml) and made basic with sodium carbonate, and the basic solution was washed twice with 25-ml portions of methylene chloride. The combined methylene chloride extracts were passed through anhydrous magnesium sulfate and the solvent was removed under reduced pressure.

Reaction products were analyzed by integration of the individual and characteristic absorptions of each compound by pmr spectroscopy in carbon tetrachloride or chloroform-d_1. Integrations were maximized and averaged over several integrations of the same signal. A measured amount of an internal standard, usually 1,2-dibromoethane or nitromethane, was used for each analysis. Individual products were identified either from the pmr spectrum of the reaction solution and from glpc retention times and peak enhancement, or after isolation by glpc using appropriate spectral methods. Protonated imines were identified prior to work-up by comparison to authentic samples prepared in acetonitrile by adding an equivalent amount of FSO_3H–SbF_5 to the imine. Pmr spectra in acetonitrile at 37° were similar to those previously reported:[21] $C_6H_5CH{=}NHC(C_6H_5)_3^+$, δ 8.85 (d, CH=N, $J_{CH=NH}$ = 18 Hz); $C_6H_5CH{=}NHCH(C_6H_5)_2^+$, δ 12.0 (broad, NH), 8.94 (d, CH=N, $J_{CH=NH}$ = 17 Hz), 6.62 (d, CHN, J_{CHNH} = 6 Hz); $C_6H_5CH{=}NHCH_2C_6H_5^+$, δ 12.7 (broad, NH), 9.01 (CH=N, $J_{CH=NH}$ = 18.5 Hz, J_{CHCH_2} = 1.0 Hz), 5.12 (CH_2N, J_{CH_2NH} = 6.0 Hz); $C_6H_5CH{=}NHC(CH_3)_3^+$, δ 8.80 (d, CH=N, $J_{CH=NH}$ = 18.3 Hz); $C_6H_5CH{=}NHCH_3^+$, δ 8.85 (CH=N, $J_{CH=NH}$ = 18, J_{CHCH_3} = 1 Hz), 3.63 (CH_3N, J_{CH_3NH} = 5 Hz).

***N*-Benzylidenebenzylamine-α-d_2.**—Benzylamine-α-d_2 was synthesized from benzonitrile and lithium aluminum deuteride (Ventron) in 32% yield using the procedure of Amundsen and Nelson,[22] bp 29° (0.15 Torr). No signal for the α hydrogens was observed by pmr spectroscopy. Benzaldehyde was condensed with benzylamine-α-d_2, using the procedure previously described, to give *N*-benzylidenebenzylamine-α-d_2 in 73% yield: bp 107–109° (0.15 Torr); pmr (CCl_4) δ 8.38 (s, 1, CH=N), 8.0–7.1 (m, 10, Ph). The ir spectrum was consistent with the structure.

Treatment of the deuterated imine with $NO^+BF_4^-$ in anhydrous acetonitrile according to the general procedure gave, by pmr analysis prior to quenching, a 42% yield of "protonated" imine (pmr δ 8.92 for $CH{=}N^+$, J = 18 Hz; no signal was observed between δ 7.0 and 4.0) and 26% of benzaldehyde (pmr δ 10.0 for CH=O). An absorption for the $C{=}NH^+$ of the protonated imine was observed as a broad signal (δ 11.5–10.8) and integrated to only one-half the value for the $CH{=}N^+$ signal; with undeuterated imine these signals have the same area. After quenching with water and after work-up no signal between δ 7.0 and 4.0 was detected by pmr spectroscopy; *N*-benzylacetamide-α-d_2 was detected by glpc analysis and confirmed by pmr spectroscopy. With triethylsilane quenching (5 equiv) the product corresponding to dibenzyl ether was collected by glpc and identified by pmr spectroscopy, δ 7.27 (s, 10.0) and 4.53 (s, 2.0).

Nitrosation of Pyridines and Other Heterocyclic Compounds.—Compounds were commercially available. The same general procedure as that given for the imines was used. With 2,4,6-trimethylpyridine, reactions were run at 25° and at 60° for between 1 and 3 hr, in acetonitrile, nitromethane, or without solvent, and with 1, 2, and 10 equiv of $NO^+BF_4^-$; only the pyridinium salt was detected prior to quenching by pmr and ir spectroscopy. The corresponding pyrylium salt would have been detected by these methods. 2,4,6-Trimethylpyrylium tetrafluoroborate was commercially available. 2,4,6-Trimethylpyridinium tetrafluoroborate was isolated from several reactions and characterized by comparison to the authentic sample by pmr and ir spectroscopy and from its melting point (233–235°). Similar reactions were attempted with 2,4,6-triphenylpyridine and gave identical results.

The reactions of $NO^+BF_4^-$ with imidazole, *N*-methyl- and *N*-benzylimidazole, 2,5-diphenyloxazole, benzoxazole, benzothiazole, phenazine, and 1*H*-1,2,4-triazole were carried out in a manner analogous to that for the pyridines. *N*-Methylimidazole and 2,5-diphenyloxazole were studied under the greatest variety of reaction conditions. Only the corresponding protonated compound could be detected.

Protonated substrates were prepared by adding the nitrogen heterocycle to a slight molar excess of fluoroboric acid in benzene. The water from the 40% aqueous fluoroboric acid was removed using a Dean–Stark trap, and the benzene was distilled under reduced pressure.

Registry No.—*N*-Benzylidenetriphenylmethylamine, 38662-28-1; *N*-benzylidenebenzhydrylamine, 36728-52-6; *N*-benzylidenebenzylamine, 780-25-6; *N*-benzylidene-*tert*-butylamine, 6852-58-0; *N*-benzylidenebenzhydrylamine, 622-29-7; nitrosonium tetrafluoroborate, 14635-75-7; 2,4,6-trimethylpyridine, 108-75-8; 2,4,6-triphenylpyridine, 580-35-8; *N*-benzylidenebenzylamine-α-d_2, 38662-32-7.

Acknowledgment.—We gratefully acknowledge the support of the National Science Foundation (Grant No. GP-27587) and of the Research Corporation for this work. We wish to thank Mr. J. Gregory Kalmbacher for preliminary studies with pyridines.

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(22) L. H. Amundsen and L. S. Nelson, *ibid.*, **73**, 242 (1951).

A Comparison of the Synthetic Utility of *n*-Butyllithium and Lithium Diisopropylamide in the Metalations of *N,N*-Dialkyltoluamides[1a]

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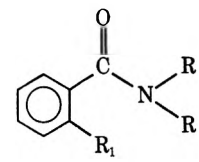
N,N-Diisopropyl-*o*-toluamide (**1**) underwent side-chain metalation using either *n*-butyllithium or lithium diisopropylamide as the lithium reagent. Evidence for the presence of lithiated *N,N*-diisopropyltoluamide was obtained by quenching studies and by using condensation reactions with benzophenone and *n*-butyl bromide. The analogous meta and para *N,N*-diisopropyltoluamides underwent predominantly a carbonyl addition reaction with *n*-butyllithium, giving the cleavage products on hydrolysis. In contrast, lithium diisopropylamide metalated both these toluamides at the respective side chain methyl in good to excellent yields. The corresponding *N,N*-diethyl-*o*-, *m*-, and *p*-toluamides were also metalated at the respective side chain positions using lithium diisopropylamide in fair to good yields.

Metalations and subsequent condensations at the methyl group of *N,N*-dimethyl-*p*-toluenesulfonamide by means of sodium amide in liquid ammonia[3] and at the ortho position of *N,N*-dimethylbenzenesulfonamide with *n*-butyllithium[4] have been observed. Unlike the sulfonamides, which are stable to nucleophilic addition and cleavage by *n*-butyllithium, *N,N*-dialkylbenzenecarboxamides undergo addition reactions with Grignard[5] and lithium reagents,[6] leading to the formation of ketones. For example, valerophenone was obtained in 70% yield when *N,N*-dimethylbenzamide was treated with *n*-butyllithium in tetrahydrofuran (THF)–hexane.[7] However, ortho and side-chain metalations have been observed when N-substituted benzamides[7] and *o*-toluamides[8] were treated with 2 equiv of *n*-butyllithium. Apparently, the initial N-metalation of the amino hydrogen deactivates the carbonyl group to attack by the base.

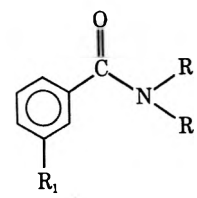
It was of initial interest during this investigation to determine if carbonyl addition of the lithium reagent to the *N,N*-dialkyltoluamides could be eliminated or significantly reduced by increasing the steric requirements of the *N,N*-dialkyl substituents; that is, could the carbonyl addition reaction be reduced or eliminated by steric factors rather than by electronic deactivation as shown by the dimetalation of N-substituted amides[7,8] described above. Secondly, the synthetic value of metalating *N,N*-dialkyltoluamides by different lithium reagents was investigated.

Results

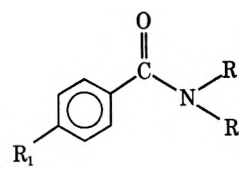
The findings of the present study show that ortho toluamide **1** (R = isopropyl) will undergo preferential side-chain metalation with *n*-butyllithium in THF at 0°, whereas para toluamide **3** (R = isopropyl), under the same metalating conditions, apparently undergoes more carbonyl addition with *n*-butyllithium than metalation.



1, R = $CH(CH_3)_2$; R_1 = CH_3
4, R = $CH(CH_3)_2$; R_1 = $CH_2COH(C_6H_5)_2$
7, R = $CH(CH_3)_2$; R_1 = $(CH_2)_4CH_3$
7′, R = $CH(CH_3)_2$; R_1 = $CH(C_4H_9)_2$
10, R = CH_2CH_3; R_1 = CH_3
13, R = C_2H_5; R_1 = $CH_2COH(C_6H_5)_2$
16, R = C_2H_5; R_1 = $(CH_2)_4CH_3$
16′, R = C_2H_5; R_1 = $CH(C_4H_9)_2$



2, R = $CH(CH_3)_2$; R_1 = CH_3
5, R = $CH(CH_3)_2$; R_1 = $CH_2COH(C_6H_5)_2$
8, R = $CH(CH_3)_2$; R_1 = $(CH_2)_4CH_3$
11, R = CH_2CH_3; R_1 = CH_3
14, R = CH_2CH_3; R_1 = $(CH_2)COH(C_6H_5)_2$
17, R = CH_2CH_3; R_1 = $(CH_2)_4CH_3$



3, R = $CH(CH_3)_2$; R_1 = CH_3
6, R = $CH(CH_3)_2$; R_1 = $CH_2COH(C_6H_5)_2$
9, R = $CH(CH_3)_2$; R_1 = $(CH_2)_4CH_3$
12, R = CH_2CH_3; R_1 = CH_3
15, R = CH_2CH_3; R_1 = $CH_2COH(C_6H_5)_2$
18, R = CH_2CH_3; R_1 = $(CH_2)_4CH_3$

Evidence of this difference in the site of attack by *n*-butyllithium in toluamides **1** and **3** was obtained initially by glpc analysis of the respective reaction mixtures, obtained by adding *n*-butyllithium dropwise to a THF solution of the respective toluamide at 0°. The glpc data of the quenched toluamides (*cf.* Table I,

(1) (a) Supported by the National Institutes of Health Grant No. CA 04455-11 from the National Cancer Institute, and by the National Science Foundation COSIP Grant No. GY-7677; (b) Department of Chemistry, VMI, Lexington, Va. 24450.

(2) (a) This work represents part of the research of J. S. G., partially fulfilling the requirements for the Ph.D. degree at Duke University; (b) Undergraduate participant in NSF–COSIP program at VMI; (c) Deceased, January 6, 1970.

(3) F. H. Rash and C. R. Hauser, *J. Org. Chem.*, **32**, 3379 (1967).

(4) H. M. Watanabe, unpublished data, 1970.

(5) See E. E. Royals, "Advanced Organic Chemistry," Prentice-Hall, Englewood Cliffs, N. J., 1954, p 582.

(6) V. Boekelheide and R. J. Windgassen, *J. Amer. Chem. Soc.*, **86**, 2020 (1958).

(7) W. H. Puterbaugh and C. R. Hauser, *J. Org. Chem.*, **29**, 853 (1964).

(8) R. L. Vaulx, W. H. Puterbaugh, and C. R. Hauser, *J. Org. Chem.*, **29**, 3514 (1964).

SCHEME I

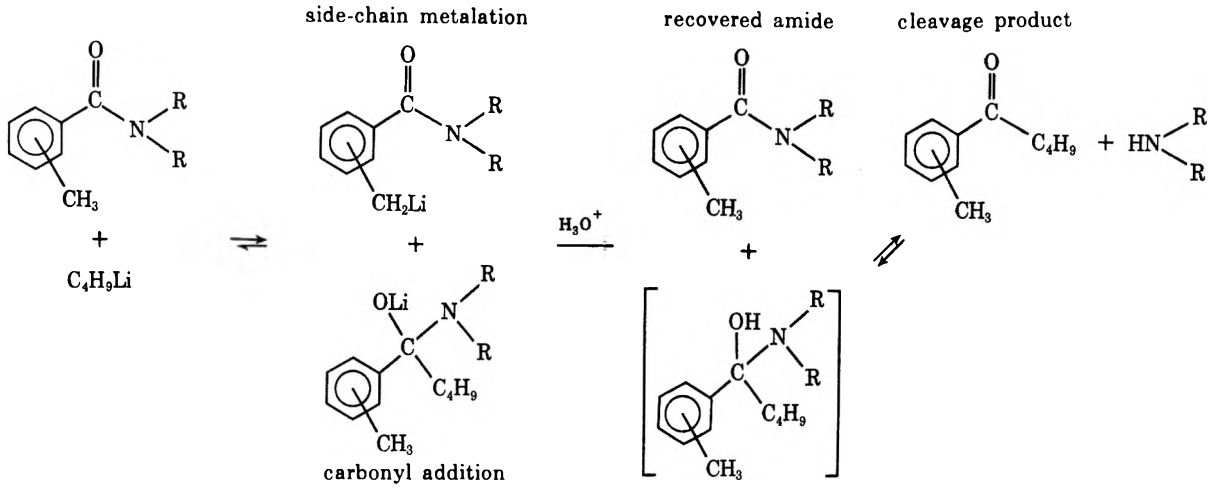


TABLE I

COMPOSITION OF THE REACTION MIXTURES[a] OF THE METALATED *N,N*-DIALKYLTOLUAMIDES WHEN QUENCHED WITH WATER

Expt	Toluamide	Metalating conditions	Carboxamide,[b] %	Ketone,[c] %	Other,[d] %
1	1	*n*-C_4H_9Li–Hexane; THF 0°	92–94	0–2	4
2	2	*n*-C_4H_9Li–Hexane; THF 0°	42	45	13
3	3	*n*-C_4H_9Li–Hexane; THF 0°	25–40	75–50	0–10
4	3	$LiN[CH(CH_3)_2]_2$; THF 0°	98	1	
5	10	*n*-C_4H_9Li–Hexane; THF 0°	68–70	20–23	8–10
6	11	*n*-C_4H_9Li–Hexane; THF 0°	20	70	10
7	12	*n*-C_4H_9Li; THF 0°	0–10	80–90	0–10

[a] Glpc analysis *via* ratio of peak areas found by integration. [b] While this term includes both unchanged carboxamide as well as the hydrolyzed side-chain metalated product, a comparison of these data to the yield data for the benzophenone and butylation reactions (Tables II and III) gives a good indication of the extent to which side-chain lithiation is occurring in the respective toluamides. [c] This term gives good indication of the extent of carbonyl addition which is occurring in the respective toluamides by the *n*-butyllithium. [d] No attempt was made to isolate or identify the "other" components of the glpc analysis, though in most cases the "other" was a single high-boiling component.

expt 1 and 3) clearly show that no *o*-tolyl butyl ketone, the expected cleavage product, was present when the intermediate lithiated toluamide of **1** was quenched. Conversely, the ketone resulting from the attack of the lithium butyl at the carbonyl of toluamide **3** was the major product recovered when lithiated **3** was quenched.

Using the identical metalating conditions, *N,N*-diethyl-*o*-toluamide (**10**) showed a metalation–carbonyl addition reactivity ratio with *n*-butyllithium which was intermediate between that of toluamides **1** and **3** (*cf.* Table I, expt 5), while the corresponding *N,N*-diethyl-*p*-toluamide (**12**) underwent an exclusive carbonyl addition reaction, as indicated by the absence of toluamide **12** in the glpc of the quenched reaction mixture.

Supporting evidence for this difference in the site of attack by *n*-butyllithium in toluamides **1**, **3**, **10**, and **12** at 0° was afforded from the varying yields obtained when the respective lithiated toluamides were condensed with benzophenone. Whereas toluamide **1** afforded an 80–85% yield of adduct **4** and toluamide **10** gave a 15–25% yield of adduct **13**, no benzophenone adduct was isolated using the identical experimental conditions with either lithiated toluamide **3** or **12**.

These results indicate that sufficient steric requirements in the *N,N*-dialkyl substituents, as in toluamide **1** and to a smaller degree in toluamide **10**, will inhibit cleavage of the amide linkage by the *n*-butyllithium and allow metalation, at least in the side chain, to occur. However, in most cases *n*-butyllithium cannot be used as a metalating reagent in preparing side-chain or ortho lithio-*N,N*-dialkyltoluamides as synthetic intermediates because of the undesirable carbonyl addition by the base with subsequent cleavage of the amide bond on hydrolysis (see Scheme I).

Since lithium diisopropylamide, $LiN[CH(CH_3)_2]_2$, has been shown to be an effective metalating reagent of *o*-, *p*-, and *m*-toluic acids,[9] metalations of the corresponding *N,N*-dialkyltoluamides were attempted using this lithium reagent. With $LiN[CH(CH_3)_2]_2$ as the metalating reagent, toluamide **1** was lithiated, then condensed with benzophenone to give carbinolamide **4** in yields varying from 80 to 95%. The intermediate lithioamide of **1** was also alkylated with *n*-butyl bromide (see Table II), yielding both mono- and di-side

TABLE II

THE CARBONYL ADDITION AND ALKYLATION REACTIONS OF THE LITHIATED *N,N*-DIISOPROPYLTOLUAMIDES. COMPARISON OF THE YIELDS[a] IN ALKYLATION REACTION USING THE STEPWISE[b] AND DIRECT[c] METHOD

Expt	Toluamide	Lithiating reagent	Electrophile	Product	Yield, %
1	1	*n*-C_4H_9Li, THF 0°	$(C_6H_5)_2C{=}O$	4	75–85
2	1	*n*-C_4H_9Li, THF 15–20°	$(C_6H_5)_2C{=}O$	4	45–50
3	1	$LiN[CH(CH_3)_2]_2$, THF 0°	$(C_6H_5)_2C{=}O$	4	80–90
4[b]	1	$LiN[CH(CH_3)_2]_2$, THF 0°	*n*-C_4H_9Br	7	70
				7′	14
4′[c]	1	$LiN[CH(CH_3)_2]_2$, THF 0°	*n*-C_4H_9Br	7	72
				7′	11
5	2	$LiN[CH(CH_3)_2]_2$, THF 0°	$(C_6H_5)_2C{=}O$	5	3–10
6[b]	2	$LiN[CH(CH_3)_2]_2$, THF 0°	*n*-C_4H_9Br	8	66
6′[c]	2	$LiN[CH(CH_3)_2]_2$, THF 0°	*n*-C_4H_9Br	8	77
7	3	*n*-C_4H_9Li, THF 0°	$(C_6H_5)_2C{=}O$	6	0–5
8	3	$LiN[CH(CH_3)_2]_2$, THF 0°	$(C_6H_5)_2C{=}O$	6	80–100
9[b]	3	$LiN[CH(CH_3)_2]_2$, THF 0°	*n*-C_4H_9Br	9	93
9′[c]	3	$LiN[CH(CH_3)_2]_2$, THF 0°	*n*-C_4H_9Br	9	87–92

[a] By glpc analysis by integration of peak areas. [b] Formation of lithioamide followed by treatment with 1-bromobutane. [c] Addition of base to a mixture of toluamide and 1-bromobutane.

(9) P. L. Creger, *J. Amer. Chem. Soc.*, **92**, 1396 (1970).

chain alkylated products, **7** and **7'**. Using the same metalating conditions *p*-toluamide **3** was metalated at the *p*-methyl group as evidenced by benzophenone condensation of the intermediate lithiated amide to give carbinolamide **6** (85–95%), and by butylation to give substituted toluamide **9** (see Table II).

Carbinolamines **4** and **6** were readily isolated from the respective reaction mixtures (see Experimental Section). However, when *m*-toluamide **2** (R = isopropyl) was metalated using $LiN[CH(CH_3)_2]_2$, then condensed with benzophenone under the exact conditions which gave carbinolamides **4** and **6** in >85% yield, only a small amount of solid product, identified as carbinolamide **5**, was isolated. This seemed to indicate that either metalation of **2** was not occurring, or that the resulting lithioamide did not condense as readily with benzophenone as did the *o*- and *p*-*N*,*N*-diisopropyltoluamides. Presumably, the latter explanation is more correct than the former, since butylation of the intermediate meta-lithiated toluamide of **2** gave 60–70% of alkylated amide **8**.

As the metalations of *N*,*N*-diisopropyltoluamides **1**, **2**, and **3** proceeded satisfactorily using $[(CH_3)_2CH]_2NLi$ as the metalating reagent, metalations of the analogous *N*,*N*-diethyltoluamides **10**, **11**, and **12** were attempted using the same lithium reagent. Under these conditions, **10** was successfully metalated at the 2-methyl position, as shown by the 50–60% yield of benzophenone adduct **13** and the 70–75% yield of mono- and di-side chain butylated amides **16** and **16'**. Similarly, *N*,*N*-diethyltoluamides **11** and **12** were successfully metalated at the respective side-chain methyl groups, with the resulting lithiated intermediates being condensed with benzophenone and/or alkylated with *n*-butyl bromide. The results are summarized in Table III.

TABLE III
THE CARBONYL ADDITION AND ALKYLATION REACTIONS OF THE LITHIATED *N*,*N*-DIETHYLTOLUAMIDES. COMPARISON OF THE YIELDS[a] IN ALKYLATION REACTIONS USING THE STEPWISE[b] AND DIRECT[c] METHODS

Expt	Toluamide	Lithiating reagent	Electrophile	Product	Yield, %
1	**10**	*n*-C_4H_9Li, THF 0°	$(C_6H_5)_2C{=}O$	**13**	15–25
2	**10**	$LiN[CH(CH_3)_2]_2$, THF 0°	$(C_6H_5)_2C{=}O$	**13**	50–60
3[b]	**10**	$LiN[CH(CH_3)_2]_2$, THF 0°	*n*-C_4H_9Br	**16**	42
				16'	25
3'[c]	**10**	$LiN[CH(CH_3)_2]_2$, THF 0°	*n*-C_4H_9Br	**16**	75
				16'	12
4	**11**	$LiN[CH(CH_3)_2]_2$, THF 0°	$(C_6H_5)_2C{=}O$	**14**	42
5[b]	**11**	$LiN[CH(CH_3)_2]_2$, THF 0°	*n*-C_4H_9Br	**17**	75
5'[c]	**11**	$LiN[CH(CH_3)_2]_2$, THF 0°	*n*-C_4H_9Br	**17**	75
6	**12**	$LiN[CN(CH_3)_2]_2$, THF 0°	$(C_6H_5)_2C{=}O$	**15**	28–40
7[b]	**12**	$LiN[CN(CN_3)_2]_2$, THF 0°	*n*-C_4H_9Br	**18**	80
7'[c]	**12**	$LiN[CN(CH_3)_2]_2$, THF 0°	*n*-C_4H_9Br	**18**	71

[a] By glpc analysis *via* integration of peak areas. [b] Formation of lithioamide followed by treatment with 1-bromobutane. [c] Addition of base to a mixture of toluamide and 1-bromobutane.

Discussion

Both the quenching experiments (Table I) and the yields of the side-chain benzophenone adducts (Tables II and III) indicate that a greater amount of side-chain metalation is occurring in the ortho *N*,*N*-dialkyltoluamides than in either of the corresponding meta or para isomers when *n*-butyllithium is used as the lithium reagent. Furthermore, the yield of the benzophenone adduct of the *o*-toluamide was much higher when R = isopropyl (**1**) than when R = ethyl (**10**). Thus, similar to some sterically hindered ketones which do not undergo carbonyl addition reactions with *n*-butyllithium,[10] it appears that a sufficiently large *N*,*N*-dialkyl group can, at least in the ortho isomers, reduce the amount of carbonyl addition by the lithium reagent and increase the amount of side-chain metalation which occurs. Closer inspection of the data (Table II, expt 1 and 2) shows that in addition to the steric factor, the temperature at which the metalation is run also determines the reaction which occurs between the lithium butyl and the toluamide. For example, at 0° the yield of the benzophenone adduct of toluamide **1** using *n*-butyllithium as the metalating reagent was 75–85%, while at >20° the yield of the addition product under otherwise identical conditions dropped to 45–50%.

Confirmation that the steric factors do play the major role in preventing carbonyl addition is supported by the ir and nmr spectra of these toluamides and their respective benzophenone addition products. Siddall and Garner have shown that increased ortho substitution in the benzene ring attached to the carbonyl causes slower rotation about the amide bond (higher coalescence temperature).[11] That is, because of this steric inhibition of resonance, substitution decreases the effect of cross conjugation of the benzene ring with the carbonyl group, and thereby increases the double-bond character of the amide bond; note the ν O=CN< of the ortho toluamides in Table IV, especially that of benzophenone adduct **4** (ν O=CN< 1591 cm^{-1}).

In addition to these low ir absorption frequencies for the amide bond, further confirmation of the greater steric crowding in the ortho toluamides can be seen by examination of the nmr spectra of the respective toluamides. For example, the nmr study of Siddall and Garner showed two methine sets of absorptions and three methyl sets of absorptions for the *N*,*N*-diisopropyl groups in the nmr spectrum of **1** at 40°,[11] while in the present study the nmr spectrum of **4** indicates that all four methyls of the *N*,*N*-diisopropyl groups are in different chemical environments (see Experimental Section). Apparently, there is sufficient steric interaction between the *N*,*N*-diisopropyl groups and the ortho side chain substituent in **4**, owing to the reduced rotation about the carbon–nitrogen–amide bond, to hinder rotation within both *N*-isopropyl groups.

Evidence that this unusual steric interaction is a combination of the two large *N*,*N*-dialkyl groups, the ortho side-chain substituent, and the amide linkage can be seen from the following data: (1) the nmr spectra of the side-chain benzophenone adduct of *N*-isopropyl-*o*-toluamide shows a single doublet (6 H), J = 6.2 Hz, centered at δ 1.1, assigned to the two methyls of the isopropyl group; (2) the nmr spectra of the corresponding *N*,*N*-dialkyl meta and para side-chain benzophenone adducts each show a single doublet, J = 6 Hz, for all the methyls of the *N*,*N*-diisopropyl groups; (3) the nmr spectrum of the side chain benzophenone adduct of *N*,*N*-diisopropyl-*o*-toluidine at 40° shows a single doublet for all the methyls of the *N*,*N*-diisopropyl groups.

(10) (a) R. C. Fuson and J. R. Larsen, *J. Amer. Chem. Soc.*, **81**, 2149 (1959); (b) R. C. Fuson, W. C. Hammann, and P. R. Jones, *ibid.*, **79**, 928 (1957).

(11) T. H. Siddall and R. H. Garner, *Can. J. Chem.*, **44**, 2387 (1966).

TABLE IV
CARBOXAMIDE INFRARED SPECTRAL DATA[a] OF THE *N,N*-DIALKYLTOLUAMIDES

Substituent	Toluamide	R_1CH_2–C(=O)–NR′R	Toluamide	CH_2R_1–C(=O)–NR′R
		cm^{-1}		cm^{-1}
R′ = R = C_2H_5; R_1 = H	13	1611	10	1618
R′ = R = C_2H_5; R_1 = $C(C_6H_5)_2$(OH)	15	1610	4	1595
R = R_1 = H; R′ = $CH(CH_3)_2$				1647
R = H; R_1 = $C(C_6H_5)_2$(OH); R′ = $CH(CH_3)_2$				1636
R′ = R = $CH(CH_3)_2$; R_1 = H	3	1623	1	1615
R′ = R = $CH(CH_3)_2$; R_1 = $C(C_6H_5)_2$(OH)	6	1614	4	1591

[a] Data recorded on the Beckman IR-20 spectrophotometer using *ca.* 0.1 *M* chloroform solutions.

Though to a lesser extent, a similar nonequivalence in the *N,N*-dialkyl groups can be seen in the nmr spectra of toluamide **10**[11] and its side-chain benzophenone adduct **13** (see Experimental Section).

Summary

While *n*-butyllithium cannot be used as a general reagent to successfully metalate *N,N*-dialkyltoluamides, the results of this study do show that the use of lithium diisopropylamide as the metalating reagent does provide a good synthetic alternative. Though the intermediate lithiotoluamides prepared using the latter metalating reagent have been condensed only with benzophenone and alkylated only with butyl bromide, it is assumed that other electrophiles and alkylating reagents should undergo the same type of reactions with the lithiated amines.

It is also important to point out that the alkylation reactions of the respective lithiated toluamides were carried out using both a stepwise and a direct metalation procedure (see Experimental Section). The results are summarized in Tables II and III.

Both the stepwise and direct method have advantages. Somewhat higher yields of products generally resulted from the stepwise method; however, greater selective control of the product ratios was possible with the direct method by adding more alkylating reagent and base as needed.

Experimental Section

All melting points were taken in open capillary tubes on a Thomas-Hoover melting point apparatus and are uncorrected. All boiling points are uncorrected. Infrared spectra were obtained on Perkin-Elmer Model 137 and 237 spectrophotometers and a Beckman IR-20A spectrophotometer, using potassium bromide pellets (KBr) or chloroform solutions for solids, and sodium chloride plates (neat) or chloroform solutions for liquids. Nmr spectra were obtained on a Varian T-60 spectrometer using deuteriochloroform as solvent. All chemical shifts are reported in parts per million (δ) downfield from an internal tetramethylsilane (TMS) standard. Gas–liquid partition chromatography (glpc) was carried out with an F & M Model 700 chromatograph, using helium as the carrier gas and a thermal conductivity detector, with 0.25 in. × 6 ft, 3% SE-30 on 60/80 Gas Chrom Q columns. The measurement of peak areas was done with a Disc integrator attached to the recorder. Measured molar response factors, determined from known mixtures of authentic materials, agreed within ±5% of the integrated peak areas. Analyses were performed by M-H-W Laboratories, Garden City, Mich. Tetrahydrofuran (THF) was freshly distilled from lithium aluminum hydride immediately before use. The *n*-butyllithium in hexane was obtained from both Foote Mineral Co., Exton, Pa., and Alfa Inorganics, Inc., Beverly, Mass., and used as supplied. The toluyl chlorides and *N,N*-diethyl-*m*-toluamide were obtained from Aldrich Chemical Co., Cedar Knolls, N. J.

The metalation reactions were done either in a 300-ml round-bottomed flask, equipped with a side arm for nitrogen inlet, or in a 500-ml round-bottomed flask fit with a Claisen adapter; a dropping funnel was placed directly above the flask, and a condenser was placed in the other side of the Claisen adapter. In both instances, the apparatus was predried and the reactions were performed under a positive nitrogen pressure.

Preparation of the *N,N*-Diisopropyltoluamides (1–3).—One mole of the appropriate toluyl chloride in 100 ml of THF was added at room temperature to a rapidly stirred solution of 5–6 mol of diisopropylamine in 800 ml of THF. After the suspension had been stirred for 20 min, the solid amine hydrochloride was collected by suction filtration. The THF and excess amine were removed from the filtrate under reduced pressure and the resulting crude *N,N*-diisopropyltoluamide was recrystallized twice from benzene–hexane and dried before use. The following toluamides were prepared using this procedure.

N,N-Diisopropyl-*o*-toluamide (**1**) had mp 100–102°; nmr ($CDCl_3$) δ 7.20–7.00 (m, 4 H, ArH), 3.97–3.03 (m, 2 H, NCH), 2.30 (s, 3 H, $ArCH_3$), 1.57, 1.05 (2 d, 12 H, $CHCH_3$) (see ref 11).

Anal. Calcd for $C_{14}H_{21}NO$: C, 76.66; H, 9.65; N, 6.39. Found: C, 76.58; H, 9.71; N, 6.26.

N,N-Diisopropyl-*m*-toluamide (**2**) had mp 59–61°; nmr ($CDCl_3$) δ 7.25–7.00 (m, 4 H, ArH), 3.67 (sp, 2 H, NCH), 2.35 (s, 3 H, $ArCH_3$), 1.32 (d, 12 H, $CHCH_3$).

Anal. Calcd for $C_{14}H_{21}NO$: C, 76.66; H, 9.65; N, 6.39. Found: C, 76.71; H, 9.68; N, 6.29.

N,N-Diisopropyl-*p*-toluamide (**3**) had mp 85–86°; nmr ($CDCl_3$) δ 7.20–7.00 (m, 4 H, ArH), 3.68 (sp, 2 H, NCH), 2.30 (s, 3 H, $ArCH_3$), 1.33 (d, 12 H, $CHCH_3$).

Anal. Calcd for $C_{14}H_{21}NO$: C, 76.66; H, 9.65; N, 6.39. Found: C, 76.50; H, 9.61; N, 6.31.

Preparation of the *N,N*-Diethyltoluamides (10–12).—One mole of the appropriate toluyl chloride in 100 ml of THF was added to a rapidly stirred solution (0°) of 5–6 mol of diethylamine in 800 ml of THF. After the suspension had been stirred for 20 min, the solid amine hydrochloride was collected by suction filtration. The THF and excess amine were removed from the filtrate under reduced pressure and the resulting crude *N,N*-diethyltoluamide was purified by distillation.

Using the above procedure, *N,N*-diethyl-*o*-toluamide (**10**), bp 118–120° (1.5 mm) [lit. bp 160° (24 mm)],[12] *N,N*-diethyl-*m*-toluamide (**11**), bp 94° (0.2 mm) [lit. bp 160° (19 mm)],[12] and

(12) N. N. Maxim, *Bull. Soc. Chim. Romania*, **11**, 29 (1929); *Chem. Abstr.*, **24**, 94 (1930).

N,N-diethyl-*p*-toluamide (12), bp 100° (0.2 mm), mp 57–58° [lit. bp 163° (17 mm)][12] were prepared. (Spectroscopic data of these ethyl toluamides corresponds to that found in ref 11.)

Metalation of *N,N*-Dialkyltoluamides Using *n*-Butyllithium in THF.—To a solution of 2.2 g (0.01 mol) of the *N,N*-diisopropyltoluamide in 150 ml of THF, precooled to 0° in an ice bath for 45–60 min, was added 8 ml (0.013 mol) of approximately 2.25 *M* *n*-butyllithium in hexane. The resulting solution was stirred for 30–60 min, then treated with either benzophenone or *n*-butyl bromide or quenched with water.

Preparation of Lithium Diisopropylamide.—To a THF solution of 2.6 g (0.026 mol) of diisopropylamine, precooled to 0°, was added 13 ml (0.026 mol) of approximately 2.0 *N* *n*-butyllithium. The resulting clear yellow solution was stirred for 30 min; it was then assumed to contain ~0.26 mol of lithium diisopropylamide.

Metalations of *N,N*-Dialkyltoluamides Using Lithium Diisopropylamide. A.—A THF solution of 4.38 g (0.02 mol) of *N,N*-diisopropyltoluamide was added dropwise to a stirred solution of 0.026 mol of lithium diisopropylamide in THF at 0°. The resulting mixture was stirred for 30–60 min and then treated with either benzophenone or *n*-butyl bromide or quenched with water.

Using this procedure the following characteristic colors were observed for the respective lithiated toluamides: ortho, deep red solution; para, deep green solution; meta, brown solution.

B.—A THF solution of 3.82 g (0.02 mol) of *N,N*-diethyltoluamide was added dropwise to a stirred solution of 0.026 mol of lithium diisopropylamide in THF at 0°. The resulting mixture was stirred for 15–90 min and then treated with either benzophenone or *n*-butyl bromide or quenched with water.

Quenching of Intermediate Lithioamides with Water or Dilute HCl.—The magnetically stirred solutions of the respective lithiotoluamides were quenched by pouring them directly onto either ice–water or equal amounts (by weight) of ice and 3 *N* HCl. The layers were separated and the aqueous layer was extracted with several 50-ml portions of ether. The combined organic layers were dried ($MgSO_4$) and then concentrated to an oil which solidified in several instances on cooling. The solids were recrystallized (benzene–hexane) and shown by mixture melting point to be recovered starting material. The oils were analyzed by glpc (Table I) and distilled under reduced pressure to give recovered toluamides and the side-chain methyl valerophenones. Using *n*-butyllithium as the lithiating reagent, the following methylvalerophenones were isolated: 2′-methylvalerophenone, bp 84° (0.6 mm) [lit. bp 97–98° (2.0 mm)];[13] 3′-methylvalerophenone, bp 85° (0.25 mm), 2,4-dinitrophenylhydrazone mp 139–140° (lit. mp 141–142°);[14] and 4′-methylvalerophenone, bp 144° (15 mm), semicarbazone mp 198–199° (lit. mp 199–201°).[15] The yields are summarized in Table I.

Condensation of the *N,N*-Diisopropyl Side Chain Lithiotoluamides with Benzophenone.—A THF solution of 4.0 g (0.022 mol) of benzophenone was added dropwise to the respective lithiated toluamide at 0°. The resulting clear yellow solution was stirred for 30 min, then inversely neutralized onto ice. Stirring was continued until the THF had evaporated, leaving a white precipitate which was filtered, weighed, and then recrystallized. The filtrate was extracted with several 50-ml portions of ether. The combined ether extracts were combined, dried ($MgSO_4$), and then concentrated to an oil which was subjected to glpc analysis.

Preparation of Carbinol Amide 4.—Using the general procedure described above, *ca.* 8 g of white solid was obtained on evaporation of the THF. Recrystallization from benzene–hexane gave 6.0–6.4 g (75–80% yield) of carbinol amide 4, mp 159–161°. Further recrystallization from benzene–hexane gave an analytical sample: mp 161.5–162°; ir ($CHCl_3$) 1595 cm^{-1} (–NC=O); nmr ($CDCl_3$) δ 6.2–7.8 (m, 14 H, aromatic), 6.5 (s, 1 H, –OH), 3.2–4.0 [m, 3.84, $PhCH_2$ and $2HC(CH_3)_2$], 1.5 [d of d, J = 6.0 Hz, 6 H, $HC(CH_3)_2$], and 1.1 [d of d, J = 6.0 Hz, 6 H. $HC(CH_3)_2$] (see ref 11).

When this reaction was run at 15–20°, rather than at 0°, the yield of 4 dropped to ~3.9 g (~50%) crude product.

Anal. Calcd for $C_{27}H_{31}NO_2$: C, 80.76; H, 7.78; N, 3.49. Found: C, 80.68; H, 7.81; N, 3.38.

Preparation of Carbinol Amide 6.—Using the general procedure described above using *n*-butyllithium as the metalating agent, no solid product was obtained when the THF evaporated. In contrast, the reaction using $LiN(i\text{-}Pr)_2$ as the metalating reagent afforded nearly 10 g of crude brown-white solid. One recrystallization from benzene–hexane gave 6.3–7.3 g (78–93%), mp 196–198°. Further recrystallization from benzene–hexane gave an analytical sample: mp 197–198°; ir ($CHCl_3$) 1614 cm^{-1} (–NC=O); nmr ($CDCl_3$) δ 6.8–7.5 (m, 14 H, aromatic), 3.3–3.9 [m, 2 H, 2 $HC(CH_3)_2$], 3.6 (s, 2 H, $PhCH_2$–), 2.6 (s, 1 H, OH), 1.3 [d, J = 6 Hz, 12 H, 2 $HC(CH_3)_2$].

Anal. Calcd for $C_{27}H_{31}NO_2$: C, 80.76; H, 7.78; N, 3.49. Found: C, 80.83; H, 7.69; N, 3.48.

Preparation of Carbinol Amide 5.—Using the general procedure described above using only lithium diisopropylamide as the metalating agent, no solid product was obtained when THF evaporated. The resulting aqueous layer was extracted with several 50-ml portions of chloroform. The combined organic extracts were concentrated to give a yellow oil. This oil was washed with several portions of petroleum ether (bp 30–60°) at room temperature to remove excess benzophenone. Crystallization occurred after the oil was allowed to stand for several days. Two recrystallizations of the solid from benzene–hexane gave 2.0 g (12%) of white, crystalline *m*-(2-hydroxy-2,2-diphenylethyl)-*N,N*-diisopropylbenzamide (5): mp 160–161°; ir (KBr) 1613 cm^{-1} (–NC=O); nmr ($CDCl_3$) δ 6.7–7.6 (m, 14.3 H, aromatic), 3.78 (s, ~2 H, $PhCH_2$–), 3.2–4.0 [m, ~2 H, 2 $HC(CH_3)_2$], 2.70 (s, 1 H, –OH), 1.25 [d, J = 6 Hz, 11.9 H, 2 $HC(CH_3)_2$].

Anal. Calcd for $C_{27}H_{31}NO_2$: C, 80.76; H, 7.78; N, 3.49. Found: C, 81.07; H, 7.76; N, 3.42.

Alkylation of Lithioamide 1′ with 1-Bromobutane (Stepwise Method).—A solution containing 12 g (0.088 mol) of 1-bromobutane in 40 ml of THF was added during 30 min to a stirred solution (0°) containing 0.060 mol of lithioamide 1′. After it had been stirred for 1 hr, the yellow solution was poured on a mixture of ice and 3 *N* HCl. The layers were separated, and the aqueous layer was extracted with several 50-ml portions of chloroform. The combined extracts were concentrated to give 16.0 g of a light yellow oil. A glpc analysis of this oil indicated a ratio of toluamide 1 to two product peaks of 16:70:14.

Purification was effected by a two-step distillation. The oil was first refluxed in a 19-cm column under reduced pressure (0.2 mm). The toluamide 1 solidified at the top of the column, and refluxing was continued until a glpc analysis of the material in the distillation flask indicated that no toluamide 1 remained. Distillation of the remaining oil with a spinning-band column gave 10.1 g (62%) of colorless *N,N*-diisopropyl-*o*-pentylbenzamide (7), bp 108° (0.2 mm), and 1.9 g (10%) of *N,N*-diisopropyl-*o*-(1-butylpentyl)benzamide (7′): mp 123–125° (0.2 mm); mp 73°; ir (neat) 1629 cm^{-1} (>NC=O); nmr ($CDCl_3$) δ 7.1–7.4 (m, 3.7 H, aromatic), 3.52 and 3.75 [m, 2 H, centers of two septets of 2 $HC(CH_3)_2$], 2.65 (t, 2 H, $PhCH_2$–), 0.67–2.0 [m, ~9 H, $+CH_2+_3CH_3$], 1.58 [d, J = 6 Hz, 12 H, 2 $HC(CH_3)_2$].

Anal. (of 7). Calcd for $C_{15}H_{29}NO$: C, 78.49; H, 10.61; N, 5.09. Found: C, 78.72; H, 10.71; N, 5.14.

7 had ir (KBr) 1621 cm^{-1} (>NC=O); nmr ($CDCl_3$) δ 7.0–7.4 (m, 3.9 H, aromatic), 3.5 and 3.75 (m, 2 H, centers of two septets of 2 $HC(CH_3)_2$], 2.75 [m, 1 H, $PhHC(CH_2-)_2$], 0.3–1.9 [m, 18 H, $2+CH_2+_3CH_3$], 1.58 [d, J = 6 Hz, 12 H, 2 $HC(CH_3)_2$].

Anal. (of 7′). Calcd for $C_{22}H_{37}NO$: C, 79.70; H, 11.25; N, 4.23. Found: C, 79.57; H, 11.46; N, 4.16.

Alkylation of *N,N*-Diisopropyl-*o*-toluamide (1) by Metalation in the Presence of 1-Bromobutane (Direct Method).—To a stirred solution containing 2.19 g (0.010 mol) of *N,N*-diisopropyl-*o*-toluamide (1) and 2.05 g (0.015 mol) of 1-bromobutane in 50 ml of THF at 0° was added during 10 min 0.010 mol of lithium diisopropylamide in THF. As the base was added to the stirred solution a red color was produced, but was rapidly discharged. A glpc analysis of an acid-neutralized sample of the reaction mixture, taken 20 min after the start of the addition of base, indicated that the solution contained toluamide 1, monoalkylation product 7, and dialkylation product 7′ in a ratio of 17:72:11, respectively. Addition of an extra 0.005 mol of base to the reaction mixture changed this ratio (glpc) to 5:75:20.

Alkylation of Lithioamide 2′ with 1-Bromobutane (Stepwise Method).—Following the stepwise procedure outlined above,

(13) P. L. Pickard and S. H. Jenkens, Jr., *J. Amer. Chem. Soc.*, **75**, 5899 (1953).

(14) E. A. Evans, *Chem. Ind. (London)*, 1596 (1957).

(15) J. H. Simons, D. I. Randall, and S. Archer, *J. Amer. Chem. Soc.*, **61**, 1795 (1939).

a light yellow oil was isolated on concentration of the organic extracts. Purification was effected by a two-step distillation (see above), giving a 64% yield of colorless *N,N*-diisopropyl-*m*-pentylbenzamide (**8**): bp 128–130° (0.2 mm); ir (neat) 1634 cm^{-1} (>NC=O); nmr ($CDCl_3$) δ 7.15 (m, 3.8 H, aromatic), 3.7 [m, 2 H, 2 $HC(CH_3)_2$], 2.62 (t, 2 H, $PhCH_2$–), 0.43–2.3 [m, 9H, $-(CH_2)_3CH_3$], 1.3 [d, J = 6 Hz, 12 H, 2 $HC(CH_3)_2$].

Anal. Calcd for $C_{18}H_{29}NO$: C, 78.49; H, 10.61; N, 5.09. Found: C, 78.36; H, 10.74; N, 5.01.

Alkylation of *N,N*-Diisopropyl-*m*-toluamide (2) by Metalation in the Presence of 1-Bromobutane (Direct Method).—Following the direct procedure described above, the reaction mixture was stirred for 2 hr, when a glpc analysis of an acid-neutralized sample of the reaction mixture indicated that the solution contained toluamide **2** and alkylation product **8** in a ratio of 33:66. Treatment of the reaction mixture with an additional 0.0075 mol of base and 0.0075 mol of 1-bromobutane changed the ratio to 23 (**2**):77 (**8**) after 2 hr.

Alkylation of Lithioamide 3′ with 1-Bromobutane (Stepwise Method).—Using the stepwise procedure described above gave a light yellow oil, glpc analysis of which showed that it contained toluamide **3** and another component in a ratio of 6:93. Purification of this crude product using two-step distillation gave an 84% yield of colorless *N,N*-diisopropyl-*p*-pentylbenzamide (**9**): bp 130–133° (0.2 mm); ir (neat) 1629 cm^{-1} (>NC=O); nmr ($CDCl_3$) δ 7.2 (m, 3.7 H, aromatic), 3.72 [m, 2 H, 2 $HC(CH_3)_2$], 2.62 (t, 2 H, $PhCH_2$–), 0.5–2.23 [m, 9 H, $-(CH_2)_3CH_3$], 1.3 [d, J = 6 Hz, 12 H, 2 $HC(CH_3)_2$].

Anal. Calcd for $C_{18}H_{29}NO$: C, 78.49; H, 10.61; N, 5.09. Found: C, 78.58; H, 10.85; N, 5.06.

Alkylation of *N,N*-Diisopropyl-*p*-toluamide (3) by Metalation in the Presence of 1-Bromobutane (Direct Method).—Following the direct procedure described above, the reaction mixture was stirred for 2 hr, when a glpc analysis of an acid-neutralized sample of the reaction mixture indicated that the solution contained toluamide **3** and alkylation product **9** in a ratio of 13:87. Treatment of the reaction mixture with an additional 0.0075 mol of base and 0.0075 mol of 1-bromobutane changed this ratio to 8 (**3**):92 (**8**).

Results with *N,N*-Diethyl-*o*-toluamide (10). Neutralization of the Lithio Intermediate with H_2O–HCl.—Using the quenching procedure described above, a light orange oil was recovered when lithium diisopropylamide was used. A glpc analysis of this oil showed the ratio of toluamide **10** to a major product to be 3:95. The major product was tentatively identified by spectral evidence as 2-(*o*-*N,N*-diethylcarbamoylphenyl)-2′-methylacetophenone: ir (neat) 1635 (amide C=O), 1705 cm^{-1} (ketone C=O); nmr ($CDCl_3$) δ 8.00–6.22 (m, 7.9 H, ArH), 4.34 (s, 1.8 H, CH_2CO), 3.42, 3.25 (12 q, 4.4 H, CH_2N), 2.45 (s, 2.7 H, $ArCH_3$), and 1.02 (t, 6.3 H, $-CH_2CH_3$).

The 2,4-dinitrophenylhydrazone derivative of this keto amide was prepared according to standard procedure[16] and recrystallized twice from ethanol–ethyl acetate to give yellow solid: mp 174–176°; nmr ($CDCl_3$) 8.3–6.8 (m, 10 H, ArH), 4.03 (s, 2 H, CH_2CO), 3.52, 2.87 (2 q, 4 H, NCH_2), 2.10 (s, 3 H, $ArCH_3$), 1.02, 0.93 (2 t, 6 H, CH_2CH_3).

Anal. (of 2,4-DNP). Calcd for $C_{26}H_{27}N_5O_5$: C, 63.79; H, 5.56; N, 14.31. Found: C, 63.60; H, 5.47; N, 14.30.

Using *n*-butyllithium as the lithiating reagent gave recovered **10** and 2′-methylvalerophenone, as shown in Table I.

Condensation of the *N,N*-Diethyl Side Chain Lithiotoluamide with Benzophenone. Preparation of Carbinol Amide 13.—Using the general procedure described above for the preparation of **4**, the reaction mixture of **10′**, after the addition of benzophenone, was stirred for 1 hr, then inversely neutralized onto ice. Using lithium diisopropylamide as the metalating reagent, *ca.* 4.2 g of crude **13** was collected on filtration after the quenched reaction mixture had been heated with a benzene–hexane solution. One recrystallization from benzene–hexane (1:2) gave a 56% yield of **13**, mp 135–136°.

Using *n*-butyllithium as the metalating reagent, the yield of carbinol amide **13** was reduced to *ca.* 20%: ir ($CHCl_3$) 1611 cm^{-1} (-NC=O); nmr ($CDCl_3$) δ 6.2–7.7 (m, 14 H, aromatic), 6.45 (s, 1 H, OH), 3.6 (s, 1.9 H, $PhCH_2$–), 3.2 and 3.57 (q, J = 7.5 Hz, ~2 H, centers of two overlapping "q" of the 2 $>NCH_2$-CH_3); 1.08 and 1.2 (t, J = 7.5 Hz, 3 H, centers of two overlapping "t" of the two, $>NCH_2CH_3$) (see ref 11).

Anal. Calcd for $C_{25}H_{27}NO_2$: C, 80.39; H, 7.29; N, 3.75. Found: C, 80.25; H, 7.40; N, 3.48.

Alkylation of Lithioamide of 10 (Stepwise Method).—Following the stepwise procedure described above, a yellow oil was isolated on concentration of the dried organic extracts. A glpc analysis of this oil indicated that the ratio of recovered toluamide **10** to two product peaks was 33:42:25.

Distillation of this oil at reduced pressure with a spinning-band column gave 5.8 g (38%) of colorless *N,N*-diethyl-*o*-pentylbenzamide (**16**), bp 102–104° (0.2 mm), and 3.5 g (20%) of colorless *N,N*-diethyl-o-(1-butylpentyl)benzamide (**16′**): bp 123° (0.2 mm); ir (neat) 1631 cm^{-1} (>NC=O); nmr ($CDCl_3$) δ 6.9–7.2 (m, 4 H, aromatic), 3.08 and 3.53 (q, 2 H, centers of two overlapping "q" of the 2 $>NCH_2CH_3$), 2.6 (t, 2 H, $PhCH_2$–), 0.7–2.0 (m, 14.8 H, $(CH_2)_3CH_3$ and 2 $>NCH_2CH_3$).

Anal. (of **16**). Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.75; H, 10.46; N, 5.84.

16 had ir (neat) 1637 cm^{-1} (>NC=O); nmr ($CDCl_3$) δ 7.0–7.5 (m, 4 H, aromatic), 2.5–4.2 [m, 5 H, $PhHC(CH_2)_2$ and 2 amido methylenes], 0.6–2.0 [m, 24 H, two $-(CH_2)_3CH_3$ and two NCH_2CH_3].

Anal. (of **16′**). Calcd for $C_{20}H_{33}NO$: C, 79.15; H, 11.14; N, 4.62. Found: C, 79.14; H, 11.14; N, 4.82.

Alkylation of *N,N*-Diethyl-*o*-toluamide by Metalation in the Presence of 1-Bromobutane (Direct Method).—To a stirred solution containing 1.91 g (0.010 mol) of *N,N*-diethyl-*o*-toluamide and 2.05 g (0.015 mol) of 1-bromobutane in 50 ml of THF at 0° was added during 10 min 0.010 mol of lithium diisopropylamide in THF. A red color was produced as the base was added to the stirred solution, but was rapidly discharged. A glpc analysis of an acid-neutralized sample of the reaction mixture, taken 20 min after the start of the addition of base, indicated that the solution contained toluamide **10**, monoalkylation product **16**, and dialkylation product **16′** in a ratio of 13:75:12, respectively. Treatment of the reaction mixture with an additional 0.005 mol of base changed this ratio to 2:76:22 after 10 min.

Results with *N,N*-Diethyl-*m*-toluamide (11). Neutralization of the Lithio Intermediate(s) with H_2O–HCl.—Using the quenching procedure described above, an orange oil was recovered when lithium diisopropylamide was used. A glpc analysis of this oil showed the ratio of toluamide **11** to the product peak to be 3:97. Distillation of the oil gave 8.0 g (86%) of 2-(*m*-*N,N*-diethylcarbamoylphenyl)-3′-methylacetophenone: bp 190° (0.25 mm); ir (neat) 1621 (amide C=O), 1675 cm^{-1} (ketone C=O); nmr ($CDCl_3$) δ 8.12–7.03 (m, 8 H, ArH), 4.23 (s, 2 H, CH_2CO), 3.35 (q, 4 H, NCH_2), 2.32 (s, 3 H, $ArCH_3$). 1.10 (t, 6 H, CH_2CH_3).

Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.48; H, 7.51; N, 4.61.

Using *n*-butyllithium as the lithiating reagent gave recovered **11** and 3′-methylvalerophenone, as shown in Table I.

Condensation of the Lithio Intermediate with Benzophenone. Preparation of Carbinol Amide 14.—A solution of 14.56 g (0.080 mol) of benzophenone in 50 ml of THF was added during 15 min to a stirred solution (0°) of the lithio intermediate. Normal work-up of the reaction mixture gave a yellow oil which was dissolved in benzene. Crystallization occurred after the solution was allowed to stand for several days and 8.5 g (42%) of a white, crystalline solid was collected. Two recrystallizations from benzene gave an analytical sample of *m*-(2-hydroxy-2,2-diphenylethyl)-*N,N*-diethylbenzamide (**14**): mp 181–183°; ir (KBr) 1618 cm^{-1} (>NC=O); nmr ($CDCl_3$) δ 6.8–7.7 (m, 13.9 H, aromatic), 3.62 (s, 2 H, $PhCH_2$), 2.9–3.65 (broad m, 3.9 H, overlapping amido methylenes), 2.62 (s, 1 H, –OH), 1.07 (t, 6.1 H, two NCH_2CH_3).

Anal. Calcd for $C_{25}H_{27}NO_2$: C, 80.39; H, 7.29; N, 3.75. Found: C, 80.20; H, 7.29; N, 3.58.

Alkylation of the Lithio Intermediate with 1-Bromobutane (Stepwise Method).—Following the stepwise procedure described above, the reaction mixture was stirred for 9 hr at room temperature, quenched, and then worked up to give a yellow oil. A glpc analysis of this oil showed that it contained toluamide **11** and one other peak in a ratio of 25:75. Distillation of the oil gave 8.8 g (60%) of colorless *N,N*-diethyl-*m*-pentylbenzamide (**17**): bp 121–122° (0.2 mm); ir (neat) 1634 cm^{-1} (>NC=O); nmr ($CDCl_3$) δ 7.18 (m, 3.8, aromatic), 3.38 (q, J = 7.5 Hz, 4 H, two N-CH_2CH_3), 2.63 (t, J = 7.0 Hz, 2.1 H, $PhCH_2$–), 0.5–2.3 [m, 15.2 H, $-(CH_2)_3CH_3$ and two $>NCH_2CH_3$].

(16) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1965, p 253.

Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.50; H, 10.38; N, 5.56.

Alkylation of *N,N*-Diethyl-*m*-toluamide (11) by Metalation in the Presence of 1-Bromobutane (Direct Method).—A solution of 0.040 mol of lithium diisopropylamide was added during 10 min to a stirred solution (0°) of 5.74 g (0.030 mol) of *N,N*-diethyl-*m*-toluamide (11) and 5.48 g (0.040 mol) of 1-bromobutane in 50 ml of THF. After it had been stirred for 3 hr, a glpc analysis of an acid-neutralized sample of the reaction mixture indicated the presence of toluamide 11 and alkylation product 17 in a ratio of 25:75.

Results with *N,N*-Diethyl-*p*-toluamide (12). Neutralization of the Lithio Intermediates with H_2O–HCl.—Using the quenching procedure described above, a copious white precipitate formed immediately when lithium diisopropylamide was employed. The solvents were removed from the mixture at reduced pressure, and the white solid was collected by vacuum filtration. The filter cake was broken up and stirred with H_2O for 5 min, and the white solid was again collected by vacuum filtration. The solid was extracted with two 200-ml portions of benzene to remove the lower molecular weight components of the mixture. After removal of the solvent, the benzene fraction gave 2.7 g of white solid. Sublimation of the solid (100°, 0.2 mm) gave 1.4 g (30%) of white, crystalline 2-(*p*-*N,N*-diethylcarbamoylphenyl)-4′-methylacetophenone: mp 110–112°; ir (KBr) 1623 (amide C=O), 1675 cm^{-1} (ketone C=O); nmr ($CDCl_3$) δ 8.17–6.90 (m, 8 H, ArH), 4.30 (s, 2 H, CH_2CO), 3.40 (q, 4 H, NCH_2), 2.38 (s, 3 H, $ArCH_3$), 1.13 (t, 6 H, CH_2CH_3).

Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.78; H, 7.59; N, 4.42.

After sublimation of the monoself-condensation product, the remaining solid was recrystallized twice from acetone to give 0.9 g (21%) of white crystalline 2-(*p*-*N,N*-diethylcarbamylphenyl)-4′-(*p*-methylphenacyl)acetophenone: mp 166–169°; ir (KBr) 1629 (amide C=O), 1678 cm^{-1} (ketone C=O); nmr (acetone-d_6) δ 8.22, 7.12 (m, 12 H, ArH), 4.47, 4.40 (2 s, 4 H, CH_2CO), 3.38 (q, 4 H, NCH_2), 2.40 (s, 3 H, $ArCH_3$), 1.10 (t, 6 H, CH_2CH_3); mass spectrum M^+ *m/e* 427.

Anal. Calcd for $C_{28}H_{29}NO_3$: C, 78.66; H, 6.84; N, 3.28; *m/e* 427.2147. Found: C, 78.78; H, 6.71; N, 2.94; *m/e* 427.2150.

Using *n*-butyllithium as the lithiating reagent gave recovered 12 and 4′-methylvalerophenone as shown in Table I.

Condensation with Benzophenone. Preparation of Carbinol Amide 15.—Using the general procedure described above for the preparation of 4, the reaction mixture of 12′, after the addition of benzophenone, was stirred for 45 min, then inversely neutralized onto ice. Using lithium diisopropylamide as the metalating reagent, 2.3–3.0 g of crude 15 were collected on filtration after the quenched reaction mixture had been heated with a benzene–hexane solution. Recrystallization from benzene–hexane (1:2) gave a 28–40% yield of 15, mp 153–154°.

Using *n*-butyllithium as the metalating reagent, no carbinol amide 15 was isolated.

15 had ir ($CHCl_3$) 1610 cm^{-1} (–NC=O); nmr ($CDCl_3$) 6.8–7.5 (m, 14 H, aromatic), 3.69 (s, 2 H, $PhCH_2$–), 3.0–3.55 (broad m, 3.9 H, two NCH_2CH_3), 2.8 (s, 0.9 H, OH), 1.1 (t, 6 H, *J* = 7 Hz, two NCH_2CH_3).

Anal. Calcd for $C_{25}H_{27}NO_2$: C, 80.39; H, 7.29; N, 3.75. Found: C, 80.52; H, 7.32; N, 3.52.

Alkylation of the Lithio Intermediates with 1-Bromobutane (Stepwise Method).—Following the stepwise procedure described above, the reaction mixture was stirred for 6 hr at room temperature, quenched, and then worked up to give a yellow oil. A glpc analysis of this oil indicated that the ratio of toluamide 12 to a product peak was 20:80.

Distillation of the oil at reduced pressure gave 9.8 g (66%) of colorless *N,N*-diethyl-*p*-pentylbenzamide (18): bp 121° (0.2 mm); ir (neat) 1629 cm^{-1} (>NC=O); nmr ($CDCl_3$) δ 7.0–7.5 (m, 3.8 H, aromatic), 3.35 (q, *J* = 7.5 Hz, 4 H, NCH_2CH_3), 2.6 (t, *J* = 7 Hz, 2 H, $PhCH_2$–), 0.62–2.1 (m, 15.2 H, $-(CH_2)_3CH_3$ and NCH_2CH_3).

Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.89; H, 10.40; N, 4.89.

Alkylation of *N,N*-Diethyl-*p*-toluamide by Metalation in the Presence of 1-Bromobutane (Direct Method).—To a stirred solution containing 1.91 g (0.010 mol) of *N,N*-diethyl-*p*-toluamide (12) and 2.05 g (0.015 mol) of 1-bromobutane in 50 ml of THF at 0° was added during 10 min 0.010 mol of lithium diisopropylamide. After the solution had been stirred for 1 hr a glpc analysis of an acid-neutralized sample showed that the reaction mixture contained toluamide 12 and alkylation product 18 in a ratio of 29:71.

Registry No.—**1,** 6641-72-1; **2,** 5448-36-2; **3,** 6937-52-6; **4,** 38630-83-0; **5,** 38630-83-0; **6,** 38630-85-2; **7,** 38630-86-3; **7′,** 38630-87-4; **8,** 38630-88-5; **9,** 38630-89-6; **10,** 2728-04-3; **11,** 134-62-3; **12,** 2728-05-4; **13,** 38631-12-8; **14,** 38631-13-9; **15,** 38631-14-0; **16,** 38631-15-1; **16′,** 38631-16-2; **17,** 38631-17-3; **18,** 38631-18-4; *n*-butyllithium, 109-72-8; lithium diisopropylamide, 4111-54-0; *o*-toluyl chloride, 933-88-0; *m*-toluyl chloride, 1711-06-4; *p*-toluyl chloride, 874-60-2; diisopropylamine, 108-18-9; diethylamine, 109-89-7; benzophenone, 119-61-9; 1-bromobutane, 109-65-9; 2-(*O*-*N,N*-diethylcarbamaylphenyl)-2′-methylacetaphenone, 38631-19-5, 38631-20-8 (2,4-DNPH); 2-(*m*-*N,N*-diethylcarbamoylphenyl)-3′-methylacetophenone, 38631-21-9; 2-(*p*-*N,N*-diethylcarbamoylphenyl)-4′-methylacetophenone, 38631-22-0; 2-(*p*-*N,N*-diethylcarbamoylphenyl)-4′-(*p*-methylphenacyl)acetophenone, 38631-23-1.

Directed Metalation Reactions. III.[1] Contribution of Oxygen Coordination in the Lithiation of *o-tert*-Butylanisole

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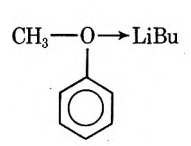
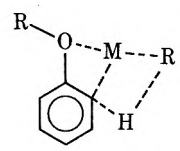
In order to ascertain the role played by coordination of the lithium ion with the oxygen atom in the metalation of anisole, *o-tert*-butylanisole was metalated with *n*-butyllithium and the position of metalation was determined. *o-tert*-Butylanisole was found to undergo metalation ortho to the methoxy group in 7.5% yield under similar conditions, which gave a 65% yield of ortho metalation of anisole itself. Addition of tetramethylethylenediamine (TMEDA), a reagent known to increase the metalating ability of *n*-butyllithium, brought about 30% metalation of *o-tert*-butylanisole. These results are attributed to steric interference by the *tert*-butyl group with the relevant coordinated intermediate; the fact that a small amount of ortho metalation was still observed is suggested to arise from the inductive effect of the methoxy group at that position.

There has been considerable speculation concerning the mechanism of the directed metalation reaction, this being one in which the alkali metal atom replaced a hydrogen at a position adjacent to the substituent on an aromatic ring. One of the primary questions raised has been the role that the heteroatom plays in such metalations. In 1946[2] it was proposed that during these metalations a coordinated complex, **1**, was formed between the heteroatom and alkyllithium reagents. Finnegan and Altshuld[3] viewed such coordination of the metal atom with the donor atom as increasing the electron-withdrawing inductive effect of the coordinating substituent. A transition state, **2**, was



1



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drawn which seemed to imply both coordination and concertedness. Thus both coordination and induction have been suggested to explain the role of the heteroatom in directed metalations.

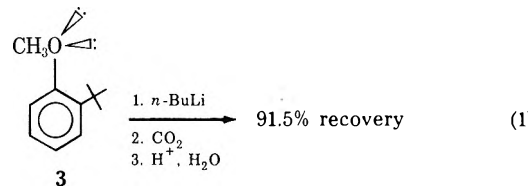
Shirley and Hendrix[4] investigated the metalation of anisole and *tert*-butyl phenyl ether with *n*-butyllithium and *tert*-butyllithium. The virtually exclusive ortho metalation observed in these reactions was interpreted to mean that such reactions had low steric requirements. These workers proposed that this low steric requirement of the metalation reaction was in disagreement with the concept of a cyclic transition state formed from a coordination complex of RLi with the heteroatom and have suggested a mechanism involving prior ionization of the metalating reagent with subsequent formation of a radical anion of the aromatic ring. This mechanism was felt to offer a better explanation of the apparent lack of steric effect observed in these systems.

Three alternative interpretations of these results of Shirley and Hendrix[4] are also possible. First, *n*-butyllithium is known to exist as a tetramer or hexamer in solution and *tert*-butyllithium has been found to be a tetramer in solution.[5] If the metalation reaction takes place with these polymeric species, rather than with the monomer, then there is very little steric difference between *n*-butyllithium and *tert*-butyllithium. Second, the greater base strength of *tert*-butyllithium may balance its possibly greater steric demand. Third, models have shown that if the methyl group of anisole is replaced by a *tert*-butyl group, there is very little additional steric interaction with the alkyllithium oligomer.

In order to ascertain the role coordination plays in the metalation reaction in the anisole system, it was decided to metalate a compound in which the possibility for coordination had been markedly reduced with respect to anisole. The compound chosen was *o-tert*-butylanisole (**3**). Space-filling models of this compound showed that the *o-tert*-butyl group restricts the possible conformers of **3** and should result in a steric hindrance to complexation.

Results and Discussion

Metalation of *o-tert*-butylanisole (**3**) with *n*-butyllithium in refluxing ether for 22 hr and condensation with Dry Ice resulted in a 91.5% recovery of starting material (eq 1). Under similar conditions, anisole is



3 (1)

converted to the ortho acid in 65% yield.[6] This is a marked reduction in reactivity relative to anisole.

Similarly, ether **3** was metalated under the same conditions and treated with trimethylsilyl chloride. The product which was isolated by vpc in 7.5% yield, was identified as a 1,2,3-trisubstituted benzene by absorptions at 5.20, 5.40, and 5.70 μ in its ir spectrum. Differentiation between **4** and **5** could not be made on these grounds. On steric grounds, however, the structure **5** is most unlikely.[7] A metalation was run for 10 hr with otherwise identical experimental conditions to check

(1) For parts I and II of this series *cf.* (a) D. W. Slocum, C. A. Jennings, T. R. Engelmann, B. W. Rockett, and C. R. Hauser, *J. Org. Chem.*, **36**, 377 (1971); (b) D. W. Slocum, B. P. Koonsvitsky, and C. R. Ernst, *J. Organometal. Chem.*, **38**, 125 (1972).

(2) J. D. Roberts and D. Y. Curtin, *J. Amer. Chem. Soc.*, **68**, 1658 (1946).

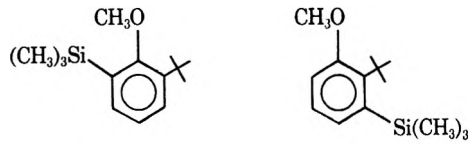
(3) R. A. Finnegan and J. W. Altshuld, *J. Organometal. Chem.*, **9**, 193 (1967).

(4) D. A. Shirley and J. P. Hendrix, *J. Organometal. Chem.*, **11**, 217 (1968).

(5) L. D. McKeever and R. Waack, *Chem. Commun.*, 751 (1969).

(6) D. A. Shirley, J. R. Johnson, Jr., and J. P. Hendrix, *J. Organometal. Chem.*, **11**, 209 (1968).

(7) C. D. Broaddus, *J. Org. Chem.*, **35**, 10 (1970).

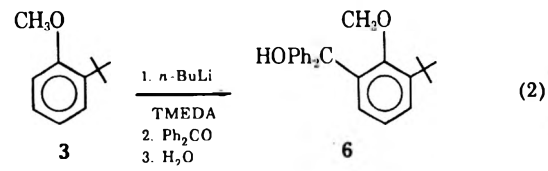


4 5

that metalation was not taking place over a shorter period, but no product was detected by vpc analysis.

The reaction of ether **3** with *n*-butyllithium and an equimolar amount of TMEDA gave a 30% yield of this same product after a 1-hr metalation period. This is in agreement with the results of Slocum, Book, and Jennings,[8] who found that TMEDA significantly increased the rate and yields of a number of directed metalation reactions.

The metalation of ether **3** with *n*-butyllithium and TMEDA followed by condensation with benzophenone gave a 25% yield of **6** (eq 2). The structure of **6** was



3 6 (2)

determined by a number of observations. Molecular models show that the anisotropic effect of two phenyl groups of an ortho-situated diphenylhydroxymethyl group should exert a distinct upfield shift on neighboring methyl resonances.[9] In the case of **6**, an upfield shift of τ 0.73 was noted for the methoxy group relative to the methoxy group of *o-tert*-butylanisole itself, supporting the validity of the structure assigned. An ir spectrum of this product showed absorptions at 5.10, 5.31, and 5.53 μ, indicative of 1,2,3-trisubstitution. This also reinforces our arguments for structure **4** being the product of the reaction of metalated ether **3** with trimethylsilyl chloride.

Concern may be expressed that the large reduction in rate of metalation of *o-tert*-butylanisole (**3**) with respect to anisole might be due to the electronic effect of the *tert*-butyl group. Although there are a number of examples of the reduction of the yields of a metalation reaction by the introduction of an alkyl substituent,[10,11] there is no precedent for an effect as large as observed here. The extreme reduction in the rate of metalation of *o-tert*-butylanisole (**3**) as compared to anisole represents another example of a reaction where a lower conversion may be explained by steric hindrance to complexation. The fact that metalation of ether **3** still occurred ortho to the methoxy group can be explained as a result of the inductive effect of the methoxy group. The increase in the rate and yield of metalation with TMEDA is probably due to the reactivity of the TMEDA-complexed (monomeric) alkyllithium being much greater than that of polymeric *n*-butyllithium. This reactive species may not need to form a complex with the heteroatom to effect metalation. The site of metalation is still ortho to the methoxy group, probably as a result of the fact that the inductive effect of the oxygen atom is strongest at that position.

(8) D. W. Slocum, G. Book, and C. A. Jennings, *Tetrahedron Lett.*, 3443 (1970).

(9) D. W. Slocum and C. A. Jennings, *J. Chem. Soc. Chem. Commun.*, 54 (1972).

(10) D. A. Shirley and E. A. Lehto, *J. Amer. Chem. Soc.*, **79**, 3481 (1957).

(11) M. Hallet and R. Huls, *Bull. Soc. Chim. Belg.*, **61**, 33 (1952).

Experimental Section

General.—*n*-Butyllithium (1.6 *M* in hexane) was purchased from the Foote Mineral Co. *N,N,N',N'*-Tetramethylethylenediamine (TMEDA), bp 120–122° (Aldrich Chemical Co.), was distilled and the fraction of bp 120.5–121.0° was collected. The redistilled TMEDA was stored over Linde 4A molecular sieves. The ether used as a reaction solvent was Matheson, Coleman and Bell "absolute" grade and was stored over Linde 4A molecular sieves. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and Alfred Bernhardt Laboratory, Mulheim, West Germany. Gas chromatography was performed on a 6-ft, 6% Apiezon L on 60–80 mesh Chromosorb W column at 155°, helium flow rate 60 cc/min. All ir spectra were obtained on a Perkin-Elmer Model 137 Infracord using the 6.246-μ band of polystyrene as a reference. The nmr spectra were obtained on a Varian A-56/60 spectrometer and a Varian HA-100 using TMS as an internal standard.

Metalation of *o-tert*-Butylanisole[12] (3). Condensation with Dry Ice.—In a flame-dried flask were placed *o-tert*-butylanisole (**3**) (3.28 g, 0.02 mol) and ether (100 ml). Under an argon atmosphere, 12 ml (0.019 mol) of 1.6 *M* *n*-butyllithium in hexane was slowly dripped in and the mixture was refluxed for 22 hr. The reaction mixture was cooled to −70° and poured into a Dry Ice–ether slush. The mixture was allowed to come to room temperature and the ether layer was separated and washed with base. The ether layer was dried over $MgSO_4$ and stripped to give *o-tert*-butylanisole (**3**) (recovery 2.98 g, 91.5%). The basic wash was acidified and extracted with ether and the ether layer was dried over $MgSO_4$ and stripped. An nmr spectrum of the resultant oil showed faint signals around τ 3, ample signals in the alkyl region, and a strong odor of valeric acid.

Metalation of *o-tert*-Butylanisole (3). Condensation with Trimethylsilyl Chloride to Produce 2-*tert*-Butyl-6-trimethylsilylanisole (4).—*o-tert*-Butylanisole (**3**) (3.28 g, 0.02 mol) was dissolved in 100 ml of dry ether. Under an argon atmosphere, 12 ml (0.019 mol) of 1.6 *M* *n*-butyllithium in hexane was added and the mixture was refluxed for 22 hr. The mixture was cooled to 0° and trimethylsilyl chloride (3.0 g, 0.0278 mol) was added over a 15-min period. The reaction was allowed to come to room temperature and was stirred for an additional 5 hr. After the reaction had been hydrolyzed with approximately 20 ml of water, the ether layer was separated and dried over $MgSO_4$ and the solvent was stripped. The resulting liquid was analyzed by vpc. The first peak was identified by its retention time as recovered *o-tert*-butylanisole (**3**). The peak whose retention time was 8.0 min with respect to *o-tert*-butylanisole was isolated. Nmr and elemental analysis data of this compound were consistent with the structure 2-*tert*-butyl-6-trimethylsilylanisole (**4**) (yield 7.2% by vpc analysis): ir 8.00 ($-OCH_3$), 8.20 [$C(CH_3)_3$], 5.20, 5.40, 5.70 μ (1,2,3-trisubstituted benzene); nmr (CCl_4) τ 2.66–3.25 (multiplet, 3.2 protons, C_6H_3-), 6.28 (singlet, 2.9 protons, $-OCH_3$), 8.59 [singlet, 9.1 protons, $-C(CH_3)_3$], 9.62 [singlet, 8.8 protons, $Si(CH_3)_3$].

Anal. Calcd for $C_{14}H_{24}OSi$: C, 70.91; H, 10.20. Found: C, 71.05; H, 10.30.

Metalation of *o-tert*-Butylanisole (3) with *n*-Butyllithium and TMEDA. Condensation with Trimethylsilyl Chloride to Produce 2-*tert*-Butyl-6-trimethylsilylanisole (4).—*o-tert*-Butylanisole (**3**) (3.28 g, 0.02 mol) and TMEDA (2.22 g, 0.0192 mol) were dissolved in 50 ml of dry ether. Under an argon atmosphere, 12 ml (0.0192 mol) of 1.6 *M* *n*-butyllithium in hexane was added. The mixture was refluxed for 1 hr and cooled to 0° and 3.0 g (0.0278 mol) of trimethylsilyl chloride was added slowly. After the mixture was stirred for an additional 4 hr at room temperature, the reaction was hydrolyzed with 20 ml of water, the layers were separated, and the ether layer was dried over $MgSO_4$ and stripped. The first peak was identified by its retention time (3.1 min with respect to ether), which was identical with that of *o-tert*-butylanisole (**3**). The peak whose retention time was 8 min with respect to *o-tert*-butylanisole was identified as 2-*tert*-butyl-6-trimethylsilylanisole on the basis of this retention time and on the fact that its nmr and ir spectra were identical with those of **4** prepared above (yield 28.8% by vpc analysis).

(12) I. J. Borowitz and G. J. Williams, *J. Org. Chem.*, **31**, 603 (1966).

Metalation of *o-tert*-Butylanisole (3) with *n*-Butyllithium and TMEDA. Condensation with Benzophenone to Produce 2-*tert*-Butyl-6-diphenylhydroxymethylanisole (6).—*o-tert*-Butylanisole (3) (3.28 g, 0.02 mol) was dissolved in 50 ml of dry ether. TMEDA (2.22 g, 0.0192 mol) was added, and under an argon atmosphere 12 ml (0.0192 mol) of 1.6 *M* *n*-butyllithium was slowly added. The mixture was stirred for 1 hr and treated with benzophenone (3.5 g, 0.0192 mol) in 20 ml of ether. The mixture was stirred for 4 hr and hydrolyzed with 20 ml of water. The ether layer was separated, washed with water, dried over $MgSO_4$, and stripped. The resulting oil was purified by heating in a steam bath overnight at 0.01 mm to remove unreacted *o-tert*-butylanisole (3) and benzophenone. An ir of the resulting oil indicated that some benzophenone still remained. The oil was subjected to steam distillation until an ir spectrum of the residue indicated that all the benzophenone had been removed. The absence of any definitive absorptions in an nmr spectrum of this residue indicated that it was contaminated by some paramagnetic material, probably a result of the steam distillation. The oil was dissolved in ether and washed through a column of sand and magnetic stirring bars. Upon removal of the solvent an oil resulted and the nmr and elemental analysis data given below were consistent with the structure 2-*tert*-butyl-6-diphenylhydroxymethylanisole (6) (yield 1.73 g, 25%): ir 2.94 (–OH), 5.10, 5.31, 5.53 (1,2,3-trisubstituted benzene), 7.90 ($-OCH_3$), 8.20 μ [$-C(CH_3)_3$]; nmr ($CDCl_3$) τ 2.59–3.63 (multiplet, 13.9 protons, $HO(C_6H_5)_2CC_6H_3-$), 6.96 (singlet, 3.2 protons, $-OCH_3$), 8.58 [singlet, 8.9 protons, $-C(CH_3)_3$].

Anal. Calcd for $C_{24}H_{26}O_2$: C, 83.02; H, 7.56. Found: C, 82.96; H, 7.75.

Registry No.—**3**, 2944-48-1; **4**, 38661-99-3; **6**, 38662-00-9; trimethylsilyl chloride, 75-77-4.

Acknowledgment.—Financial support in the form of a Southern Illinois University Graduate Fellowship for B. P. K. is gratefully acknowledged. Portions of this research were supported by the Office of Research and Projects, Southern Illinois University.

Directed Metalation Reactions. IV.[1] 2-Metalation of N-Substituted Ferrocenecarboxamides

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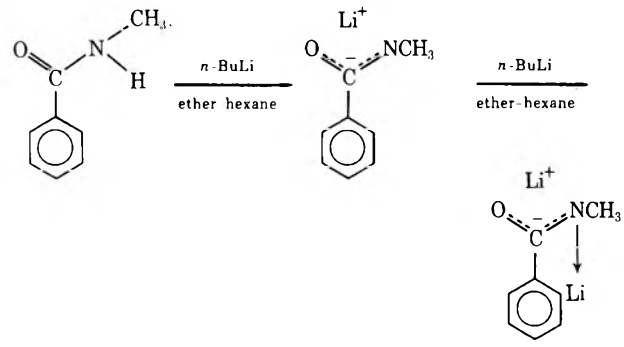
Demonstration of the 2-metalating ability of the N-substituted carboxamide group in ferrocene is presented. By means of the 2-lithiated intermediate a series of 1,2-disubstituted ferrocenes, where one of the substituents is the carboxamide group, has been prepared. That this procedure will be useful for the preparation of 2-substituted ferrocenecarboxylic acids has been shown by the three-step synthesis, starting from ferrocene, of 2-methylferrocenecarboxylic acid.

Puterbaugh and Hauser in 1963[2] demonstrated the interesting phenomenon of the directing ability of the methyl amide substituent in the 2-metalation of the benzene nucleus. This served to extend the original observation from the Hauser group of the directing ability of the dimethylaminomethyl substituent in both the benzene[3] and ferrocene[4] systems. Metalation of the amide functional group was postulated to occur by successive removal of two protons: the first from the monosubstituted amide group to produce a resonance-stabilized anion; the second from the 2 position of the benzene ring, with a coordinated lithio intermediate similar to that described for the 2-lithiation of aromatics containing the dimethylaminomethyl substituent being proposed (Scheme I). The resonance-stabilized anion which was produced by the removal of the nitrogen proton was felt to significantly reduce the tendency of the carbonyl group to undergo nucleophilic attack. Hence electrophilic attack of the more reactive second position of metalation, *i.e.*, the 2 position of the aromatic ring, could be observed.

In these laboratories we have observed that directed metalation reactions of monosubstituted benzenes can be made to occur in their ferrocene counterparts, often

SCHEME I



with greater facility.[5] These observations, coupled with our desire to examine methods of synthesizing 2-substituted ferrocene derivatives, prompted an investigation of the use of the directed metalation of *N*-ethylferrocenecarboxamide (1).

Results and Discussion

N-Ethylferrocenecarboxamide (1) was metalated with 1.5 equiv of *n*-butyllithium and condensed with various reagents in order to test the suitability of the procedure as a method of synthesizing 1,2-disubstituted ferrocenes. The *N*-ethyl derivative was chosen for examination because of its recorded preparation;[6] the

(1) For part III, *cf.* D. W. Slocum and B. P. Koonsvitsky, *J. Org. Chem.*, **38**, 1675 (1973).

(2) W. H. Puterbaugh and C. R. Hauser, *J. Amer. Chem. Soc.*, **85**, 2467 (1963).

(3) (a) F. N. Jones, M. F. Zinn, and C. R. Hauser, *J. Org. Chem.*, **28**, 663 (1963); (b) F. N. Jones, R. L. Vaulx, and C. R. Hauser, *ibid.*, **28**, 3461 (1963).

(4) D. W. Slocum, B. W. Rockett, and C. R. Hauser, *J. Amer. Chem. Soc.*, **87**, 1241 (1965).

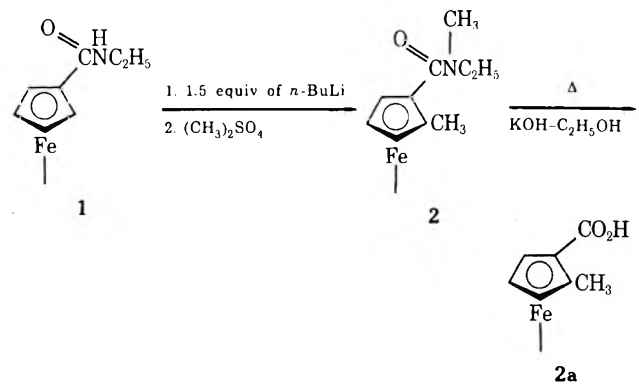
(5) *Cf.*, for example, D. W. Slocum, C. A. Jennings, T. R. Engelmann, B. W. Rockett, and C. R. Hauser, *J. Org. Chem.*, **36**, 377 (1971); D. W. Slocum, B. P. Koonsvitsky, and C. R. Ernst, *J. Organometal. Chem.*, **38**, 125 (1972).

(6) M. D. Rausch, P. Shaw, D. Mayo, and A. M. Lovelace, *J. Org. Chem.*, **23**, 505 (1958).

N-methyl derivative was later found to be accessible by the same route. That one of the two substituents of the 1,2-disubstituted ferrocene systems thus produced was an amide was of particular interest, compared to the directing groups previously studied in the ferrocene system, since numerous additional derivative possibilities could be prepared through the hydrolysis product of the amides, namely, the 2-substituted carboxylic acids. Thus the scope of the reaction was limited only by the type of electrophilic condensing reagents that would react, the ease of hydrolysis of the amide, and the reactions the derived carboxylic moiety could undergo. As we shall see, these are significant limitations to the convenience of this particular synthetic technique for the preparation of 1,2-disubstituted ferrocenes.

The ability of the *N*-ethylamide functional group to direct lithiation to the 2 position of ferrocene was demonstrated by two independent routes. The first method, shown in Scheme II, was to synthesize 2-

SCHEME II



1 2 2a

methylferrocenecarboxylic acid (**2a**) *via* the carboxamide route and match its properties with those reported for the known compound.[7] It was also found possible to prepare 2-methyldimethylaminomethylferrocene (**4**) by two separate methods (Scheme III). One of these was *via* the carboxamide route; the other was *via* the 2-lithiation of dimethylaminomethylferrocene (DMAMF) (**3**). The fact that the last-mentioned compound has clearly been demonstrated to undergo metalation in the 2 position establishes without question that the carboxamide functional group on ferrocene also directs metalation to the 2 position.

Scheme III contains two steps that deserve comment. It has been reported that certain ferrocene carboxamides cannot be hydrolyzed;[8] however, the *N*-methyl-*N*-ethylamide **2** was found to undergo basic hydrolysis but not with great ease. The two steps in Scheme III leading to 2-methyldimethylaminomethylferrocene (**4**) utilize an amine exchange reaction that was developed in this laboratory; recently Ugi and coworkers have reported a similar reaction.[9] This amine exchange procedure has proved to be convenient for the substitution of a dimethylamine functional group in place of other types of substituted amines.

The conditions found to maximize the yield of 2-methylcarboxamide **2** from the metalation of carboxamide **1** followed by derivatization with dimethyl sulfate were a mole ratio of 1.5:1.0 *n*-butyllithium/carboxamide **1** in THF solvent. Higher ratios gave significant unsubstituted ring metalation, as noted in other ferrocene systems.[4,5] A time study of the reaction showed the yield of 2-methyl carboxamide **2** to reach a maximum after 10 min. In each trial of the study 0.6 g (2.30 mmol) of *N*-ethylferrocenecarboxamide (**1**), 2.5 ml of 1.6 *M* *n*-butyllithium in ether–hexane, and 50 ml of purified, dry THF were used. The data are shown in Table I.

TABLE I

TIME STUDY OF 2-METHYLATION OF LITHIATED *N*-ETHYLFERROCENECARBOXAMIDE (**1**)

Time, min	Quantity of 2-methylcarboxamide **2**, mmol	Quantity of *N*-methyl-*N*-ethylferrocenecarboxamide **9**, mmol	Summation of the two products, mmol
1	0.49 (0.49)[a]	1.66 (1.61)	2.15 (2.10)
8	0.63	1.48	2.11
10	0.70 (0.66)	1.36 (1.36)	2.06 (2.02)
15	0.35	1.30	1.65
20	0.18 (0.21)	1.44 (1.48)	1.62 (1.69)
30	0.07	1.59	1.66

[a] Figures in parentheses represent duplicate runs.

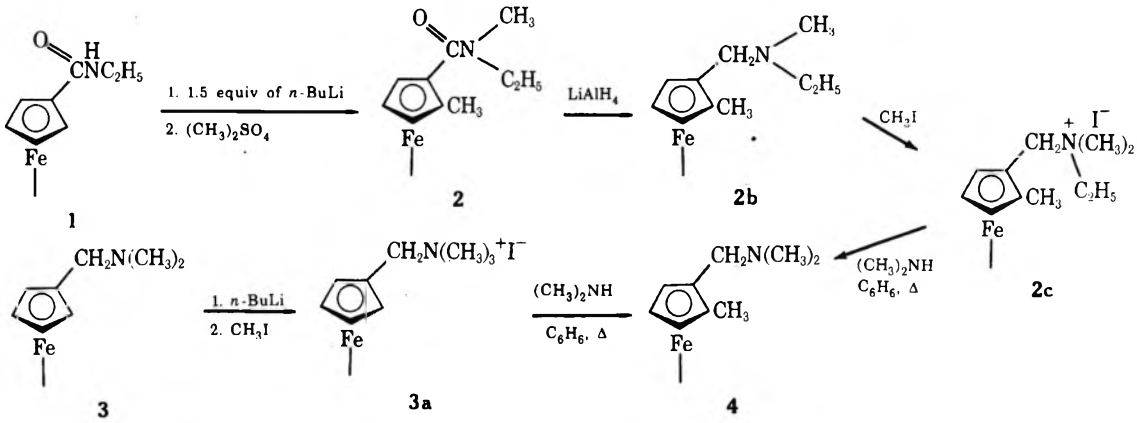
Scheme IV depicts the proposed successive removal of protons from *N*-ethylferrocenecarboxamide (**1**) necessary to explain the reported observations. The mono-N-anion **1a** could give rise to *N*-methyl-*N*-ethylferrocenecarboxamide (**9**) when treated with dimethyl sulfate. This product could also be argued to arise just as easily from incomplete derivatization of the dianion intermediate **1b**, but the fact that no product was detected arising from substitution at only the more reactive site, namely, the 2-lithio position, mitigates strongly against this supposition. The dianion **1b** would be the only path leading to 2-methyl carboxamide **2**.

The relative dianion (**1b**) and mono-N-anion (**1a**) concentrations were conveniently followed by the isolation of 2-methyl carboxamide (**2**) and N,N-disubstituted carboxamide (**9**) produced upon treatment with dimethyl sulfate. Since from Table I the dianion product can be seen to have increased at a rate similar to that for the decrease of the monoanion product over the first 10 min, it can be deduced that the 2-methyl N,N-disubstituted carboxamide **2** was derived from an equilibrium involving the mono-N-anion **1a**. After a period of 10–15 min, the dianion **1b** apparently abstracts a proton and regenerates the mono-N-anion. This seems plausible, since as further time passed the dianion product **2** decreased by the same magnitude as the mono-N-anion product **9** increased.

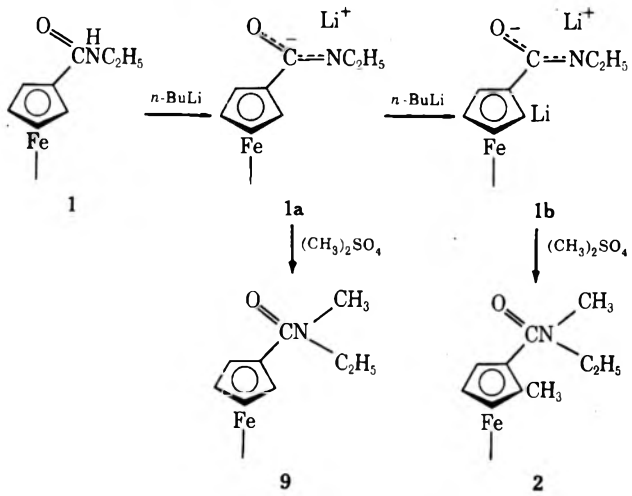
The yield of 2-methyl N,N-disubstituted carboxamide **2** falls off sharply after 10 min, as does the combined yield of products. After the maximum yield of product **2** was reached (10 min), it was observed that one-third of the starting material was lost. Up to this point the material balance had been within experimental error. Possibly a different reaction occurred at the

(7) G. Haller and K. Schlogl, *Monatsh. Chem.*, **98**, 603 (1967); H. Falk, G. Haller, and K. Schlogl, *ibid.*, **98**, 592 (1967).
(8) N. Weliky and E. S. Gould, *J. Amer. Chem. Soc.*, **79**, 2742 (1957).
(9) G. Gokel, P. Hoffmann, H. Kleimann, H. Klusacek, C. Marquarding, and I. Ugi, *Tetrahedron Lett.*, 1771 (1970).

SCHEME III



SCHEME IV



10-min point. This unknown reaction yielded no new identifiable products. After the initial decline in products was observed, the summation of the two products remained relatively constant over a 15-min interval, indicating that the competing reaction was no longer interfering. The nature of this very rapid reaction remains uncertain.

Table II lists the new 1,2-disubstituted ferrocenes which have been prepared by 2-lithiation of *N*-ethylferrocenecarboxamide (1) as a result of this investigation.

TABLE II

NEW 1,2-DISUBSTITUTED FERROCENES PREPARED FROM *N*-ETHYLFERROCENECARBOXAMIDE (1)

Compd	Molecular formula[a]	Ir spectrum, cm^{-1} [b]
2-Methyl-*N*-methyl-*N*-ethylferrocenecarboxamide (2)	$C_{16}H_{19}NOFe$	2950, 1625 (C=O), 825
2-Ethyl-*N*,*N*-diethylferrocenecarboxamide (5)	$C_{17}H_{23}NOFe$	2970, 1629 (C=O), 825
2-*n*-Propyl-*N*-*n*-propyl-*N*-ethylferrocenecarboxamide (6)	$C_{19}H_{27}NOFe$	3000, 2980, 1630 (C=O), 825
2-Trimethylsilyl-*N*-ethylferrocenecarboxamide (7)	$C_{16}H_{23}NOSiFe$	1670, 1280, 1240
2-Diphenylhydroxymethyl-*N*-ethylferrocenecarboxamide (8)	$C_{26}H_{25}NO_2Fe$	
2-Methyl-*N*,*N*-dimethylaminomethylferrocene (4)	$C_{14}H_{19}NFe$[c]	2920, 1930, 735

[a] Satisfactory analytical data were reported for all compounds listed in the table, unless otherwise noted. [b] The usual 9- and 10-μ bands indicative of homoannular substitution were found for all ferrocenes and are not recorded. [c] *Anal.* Calcd: C, 65.41; H, 7.40; N, 5.45; Fe, 21.74. Found: C, 65.98; H, 7.63; N, 5.37; Fe, 20.35.

Experimental Section

General starting materials were obtained from Matheson Coleman and Bell. Arapahoe Chemical Co. supplied the ferrocene starting materials. All starting materials were checked for purity prior to use. Foote Mineral Co. supplied the organolithium reagents. All reactions involving the use of organolithium reagents were conducted under an inert atmosphere of argon. Ethyl isocyanate was a complimentary sample supplied by Ott Chemical Co. Nmr data were obtained on a Varian A 56/60 spectrometer at 44° with internal tetramethylsilane (TMS) standard. Concentrations were approximately 10% by volume in $CDCl_3$ unless otherwise stated. All ir spectra were obtained on a Perkin-Elmer Model 137 infracord either as smears or Nujol mulls using the 6.25-μ band of polystyrene as a reference. All ferrocene compounds possessed the 9–10-μ band which was characteristic of an homoannularly unsubstituted cyclopentadiene ring. The 9–10-μ bands are underlined. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and all melting points were corrected.

Metalations were performed by injecting the requisite amount of *n*-butyllithium into a closed flask containing a side arm fitted with a septum and a water-cooled condenser fitted with a drying tube.

A. Preparation of 2-Methyl-*N*-methyl-*N*-ethylferrocenecarboxamide (2).—To a solution of 0.6 g (0.023 mol) of *N*-ethylferrocenecarboxamide (1) in 50 ml of purified THF, 2.5 ml of a 1.6 *M* solution of *n*-butyllithium was injected. The lithiation was allowed to proceed for 10 min and then 0.5 ml of dimethyl sulfate was quickly injected into the solution and the solution was allowed to stir for 30 min. The reaction mixture was evaporated to constant weight, suspended in water, and extracted with several portions of methylene chloride. Anhydrous $MgSO_4$ was used to dry the combined extracts, which were evaporated and chromatographed on basic alumina II. The product was eluted with a 50:50 mixture of petroleum ether (bp 30–60°)–methylene chloride. Three bands were observed on the chromatography column. The first band eluted was an oil weighing 0.2 g (30.4%); the following analytical data identified it as 2-methyl-*N*-methyl-*N*-ethylferrocenecarboxamide (2). The second band was also an oil, weighing 0.37 g (59%), and was identified as *N*-methyl-*N*-ethylferrocenecarboxamide (9). The third band, a red material, was isolated in only a trace amount.

Nmr data for 2-methyl-*N*-methyl-*N*-ethylferrocenecarboxamide (2): δ 1.10 (t, 8.0, J = 7.6 Hz), 2.1 (s, 3.0), 2.95 (s, 3.0), 3.40 (AB quartet, 2.0, J = 7.3 Hz), 4.18 (m, 7.9). Nmr data for *N*-methyl-*N*-ethylferrocenecarboxamide (9): δ 1.18 (t, 3.0, J = 7.5 Hz), 3.06 (s, 3.0), 3.51 (AB quartet, 2.1, J = 7.0 Hz), 4.18 (s, 5.1), 4.26 (m, 1.9), 4.59 (m, 2.0). Ir data: major peaks at 2960, 1625 (C=O), *1110*, *1000*, and 830 cm^{-1}. *Anal.* Calcd for $C_{14}H_{17}NOFe$: C, 62.03; H, 6.28; N, 5.17; Fe, 20.62. Found: C, 62.25; H, 6.32; N, 5.22; Fe, 20.46.

Preparation of 2-Methylferrocenecarboxylic Acid (2a).—A solution of 0.1 g (0.35 mol) of 2-methyl-*N*-methyl-*N*-ethylferrocenecarboxamide (2) and 20.0 g of KOH in 30 ml of 95% ethanol was refluxed under an argon atmosphere for 3 days. At the end of the first day 25 ml of 95% ethanol was added and allowed to distil from the reaction mixture. The mixture was then brought up to approximately 50 ml volume and argon was flushed through the system, which was then allowed to reflux for another day. This procedure was repeated at the end of the second day. At the end of the third day the sample was distilled almost to dryness. This mixture was then partitioned between 10% NaOH and methylene chloride. The aqueous layer was acidified with 10% H_2SO_4 and extracted several times with methylene chloride. The combined methylene chloride extracts were washed several times with water, dried over anhydrous $MgSO_4$, and evaporated to dryness to yield 0.03 g (35.2%) of crystalline acid **2a**, mp 151–153°. A sublimed sample had a melting point of 155–156° (lit.[7] mp 158–160°). Nmr data: δ 2.29 (s, 3.0), 4.17 (s, 5.0), 4.33 (m, 2.4), 4.79 (m, 1.5). The carboxyl group proton was not discernible; however, from integration it was probably broadly spread out under the δ 4.33 and 4.79 multiplet. Ir data: major peaks at 3300 (OH), 1670 (C=O), 1280, 1240, *1120*, and *1000* cm^{-1}.

Anal. Calcd for $C_{12}H_{12}O_2Fe$: C, 59.06; H, 4.92. Found: C, 59.36; H, 5.21.

Preparation of 2-Methyl DMAMF (4) from 2-Methylcarboxamide (2).—To a stirring suspension of ether and $LiAlH_4$, 1.0 g (3.5 mol) of 2-methyl-*N*-methyl-*N*-ethylferrocenecarboxamide (2) dissolved in ether was slowly added. The reaction was kept at reflux temperature for 24 hr. After this period water and 15% NaOH were added to decompose excess $LiAlH_4$. The reaction mixture was acidified and extracted with ether. The aqueous layer was then made basic and this basic solution was extracted with ether. Reduction afforded 0.8 g (82%) of 2-methyl-*N*-ethyl-*N*-methylaminomethylferrocene (**2b**). This amine was treated with an excess of methyl iodide to form the quaternary ammonium salt **2c**. The quaternary salt **2c** was subjected to an amine exchange reaction. Dimethylamine was passed for 3 days through a refluxing heterogeneous mixture of 100 ml of benzene and 1.0 g of methiodide **2c**. The reaction mixture was acidified with 10% H_2SO_4 and extracted with ether. The aqueous layer was made basic with 10% NaOH and extracted with ether. This latter ether layer was dried over anhydrous $MgSO_4$, filtered, and stripped to give 0.6 g of an oily product. This oil was chromatographed on basic alumina IV. The material was eluted with petroleum ether (trace of ether) solvent to yield 0.6 g (92%) of 2-methyl DMAMF (4).

B. Preparation of 2-Ethyl-*N*,*N*-diethylferrocenecarboxamide (5).—To a solution of 0.6 g (2.4 mmol) of *N*-ethylferrocenecarboxamide (1) in 25 ml of purified THF, 2.5 ml (1.6 *M*) of *n*-butyllithium was injected and the solution was allowed to stir for 10 min. At the end of 10 min, the mixture was quickly treated with an excess of diethyl sulfate in THF and subsequently allowed to stir for 1 hr. After the solvent had been stripped, the resulting thick oil was taken up in methylene chloride, washed several times with water, dried over $MgSO_4$, and then chromatographed on basic alumina IV with a solvent system of 50:50 petroleum ether–methylene chloride. Three bands were observed and separated. Band I was eluted as an oil and was shown to be 2-ethyl-*N*,*N*-diethylferrocenecarboxamide (**5**), 0.16 g (22%). Band II, a crystalline solid, was *N*,*N*-diethylferrocenecarboxamide (**10**), 0.35 g (53%), mp 59–60°. Band III was starting material 1, 0.15 g (25%).

Nmr data for 2-ethyl-*N*,*N*-diethylferrocenecarboxamide (**5**): δ 1.10 and 1.11 (overlapping t, 9.0, J = 7.0 Hz each), 2.46 (m, 2.0), 3.30 (m, 4.0), 4.11 and 4.21 (m and s, respectively, 8.0).

Nmr data for *N*,*N*-diethylferrocenecarboxamide (**10**): δ 1.20 (t, 6.2, J = 7.5 Hz), 3.52 (AB quartet, 3.9, J = 7.0 Hz), 4.23 (m, 7.2), multiplet centered at 4.65 (m, 1.8).

Preparation of 2-Ethyl-*N*,*N*-diethylaminomethylferrocene (5a).—To a large excess of $LiAlH_4$ suspended in a vigorously stirred solution of ether, 0.16 g (0.5 mmol) of 2-ethyl-*N*,*N*-diethylferrocenecarboxamide (**5**) dissolved in ether was slowly added. The reaction mixture was refluxed overnight. Excess $LiAlH_4$ was hydrolyzed with 10 ml of water followed by 10 ml of 10% NaOH. The solution was extracted with ether and the ether extracts were evaporated to a dark oil, which was chromatographed with petroleum ether on basic alumina IV yielding 0.14 g (98%) of amine **5a** as an oil. Nmr data: δ 1.06 (m, 9.0), 2.38 (m, 6.1), 3.42 (AB quartet, 2.0, ν_1 = 3.31, ν_2 = 3.54, J = 13.5 Hz), 4.00 (m, 8.3). Ir data: major peaks at 3010, *1110*, *1000*, and 830 cm^{-1}.

Preparation of 2-Ethyl DMAMF (5b).—2-Ethyl-*N*,*N*-diethylaminomethylferrocene (**5a**) (0.14 g) was treated with methyl iodide, producing the quaternary ammonium salt. The salt was filtered, dried, and found not to possess a sharp melting point. This quaternary salt was refluxed in benzene–dimethylamine for 3 days to produce 0.08 g of crude oil product. The oil was chromatographed on basic alumina IV; 0.01 g (7.7%) of an oil identified as 2-ethyl DMAMF (**5b**) was eluted. Physical and spectral properties of this oil were in accord with those reported by Nesmeyanov and coworkers[10] for this compound prepared by a less direct method. Nmr data: δ 1.17 (t, 3.0, J = 7.5 Hz), 2.27 (AB quartet and s, 8.1, J = 7.5 Hz), 3.25 (AB quartet, 2.0, ν_1 = 3.16, ν_2 = 3.35, J = 12.5 Hz).

C. Preparation of 2-*n*-Propyl-*N*-ethyl-*N*-*n*-propylferrocenecarboxamide (6).—To a stirring solution of 4.0 g (0.015 mol) of *N*-ethylferrocenecarboxamide (1) in THF, 20.0 ml (0.03 mol) of *n*-butyllithium was injected. The solution was allowed to react for 10 min and quickly treated with an excess of di-*n*-propyl sulfate. The reaction was allowed to stir for 1 hr at room temperature and hydrolyzed with water. The aqueous THF solution was stripped under vacuum and the resultant thick oil was taken up in ether and washed with water several times. The ether layer was dried over $MgSO_4$ and evaporated to a thick oil, which was chromatographed on a 50:50 mixture of alumina I–alumina IV using a 50:50 mixture of methylene chloride–petroleum ether, yielding first starting material (90% recovery) and 0.4 g (7.6%) of 2-*n*-propyl-*N*-ethyl-*N*-*n*-propylferrocenecarboxamide (**6**). Nmr data: δ 0.61–1.68 (m, 13.2), 2.13–2.45 (m, 1.9), 2.80–3.40 (m, 3.9), 4.08 (m, 8.0).

D. Preparation of 2-Trimethylsilyl-*N*-ethylferrocenecarboxamide (7).—To a stirring solution of 0.6 g (2.34 mmol) of *N*-ethylferrocenecarboxamide (1) in 25 ml of THF, 2.5 ml (1.6 *M*) of *n*-butyllithium was quickly added. The mixture was allowed to stir under an argon atmosphere for 10 min. Trimethylchlorosilane (1.5 ml, 0.014 mol) was added and allowed to stir for 1 hr. To ensure complete removal of THF, the reaction mixture was evaporated to dryness repeatedly with subsequent additions of methylene chloride. The material was then extracted several times with a water–methylene chloride system. The methylene chloride portion was dried with anhydrous $MgSO_4$, filtered, and evaporated to dryness. The solid material obtained was subjected to column chromatography on alumina IV. 2-Trimethylsilyl-*N*-ethylferrocenecarboxamide (**7**) was the first material eluted from the column with a solvent system of 50:50 petroleum ether–methylene chloride, 0.09 g (12.3%), mp 139–141°. Nmr data: δ 0.33 (s, 9.0), 1.22 (t, 2.9, J = 7.0 Hz), 4.17 (s, 5.1), 4.26 (m, 0.9), 4.40 (m, 1.0), 4.60 (m, 1.0).

E. Preparation of 2-Diphenylhydroxymethyl-*N*-ethylferrocenecarboxamide (8).—To a solution of 0.6 g (2.4 mmol) of *N*-ethylferrocenecarboxamide (1) in 50 ml of purified THF, 2.5 ml (1.6 *M*) of *n*-butyllithium was quickly added and the solution was allowed to stir for 10 min. The reaction was then treated with an excess of benzophenone in THF and allowed to stir for 12 hr. The solvent was removed by vacuum distillation, yielding a thick, syrupy material which was dissolved in ether and washed several times with water. The ether layer was dried with $MgSO_4$ and evaporated to dryness. The material was chromatographed on basic alumina IV with a 50:50 petroleum ether–methylene chloride solvent system and the products were eluted in the following order: 0.49 g (82%) starting material 1, 0.05 g (5%) 2-diphenylhydroxymethyl-*N*-ethylferrocenecarboxamide (**8**), mp 245–246°, and a trace of a red colored material. Nmr data: δ 0.96 (t, 3.0, J = 7.0), 3.15 (quartet, 2.0) 3.66 (m, 0.9), 4.38 (m, 7.0), 5.91 (s, 1.0), 7.38 (m, 10.0), 8.21 (s, 1.0).

F. Preparation of 2-Methyl DMAMF (4) *via* Amine Exchange Reaction.—Dimethylamine was passed for 3 days through a refluxing heterogeneous mixture of 100 ml of benzene and 1.0 g of the 2-methylmethiodide of DMAMF (**3a**).[11] The reaction mixture was acidified with 10% H_2SO_4 and extracted with ether. The aqueous layer was made basic with 10% NaOH and extracted with ether. This latter ether layer was dried over anhydrous $MgSO_4$, filtered, and stripped to give 0.6 g of an oily product.

(10) L. S. Shilovtseva, E. G. Perevalova, V. A. Nefedov, and A. N. Nesmeyanov, *Dokl. Akad. Nauk SSSR*, **7**, 2175 (1966).

(11) D. W. Slocum, W. E. Jones, T. F. Crimmins, and C. R. Hauser, *J. Org. Chem.*, **34**, 1973 (1969).

This oil was chromatographed on basic alumina IV. The material was eluted with petroleum ether (trace of ether) solvent to yield 0.6 g (92%) of 2-methyl DMAMF (4). Nmr data: δ 1.95 (s, 3.0), 2.13 (s, 6.0), 3.26 (AB quartet, 2.1, $\nu_1 = 3.21$, $\nu_2 = 3.30$, $J = 13.0$), 4.00 (m, 8.0).

Registry No.—**1**, 38744-26-2; **2**, 38641-31-5; **2a**, 12214-99-2; **4**, 12111-28-3; **5**, 38641-34-8; **5a**, 38641-35-9; **5b**, 12111-89-6; **6**, 38641-37-1; **7**, 38641-38-2; **8**, 38641-39-3.

Oxidation of Olefins by Palladium(II). VI. Ethylene Oxidation by Palladium(II) Acetate in Acetic Acid Promoted by Various Oxidants[1]

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Palladium(II) salts alone in acetic acid oxidize ethylene to vinyl acetate. It has been previously reported that $CuCl_2$ and NO_3^- increase the rate of oxidation and change the product from vinyl acetate to 1,2-disubstituted ethanes such as ethylene glycol mono- and diacetate and 2-chloroethyl acetate. The present study was undertaken to determine the generality of this new reaction. A number of oxidants, including $K_2Cr_2O_7$, $NaNO_2$, $CuBr_2$, MnO_2, $Pb(OAc)_4$, $Tl(OAc)_3$, $TlCl_3$, and $HAuCl_4$, were also found to be active in this reaction. Others which had little or no activity include *p*-quinone, $FeCl_3$, $Fe(OAc)_3$, $Hg(OAc)_2$, $MoCl_5$, and $MoOCl_4$. $CuBr_2$ gave 2-bromoethyl acetate. In addition to the 1,2-disubstituted ethanes, $Tl(OAc)_3$, $TlCl_3$, and $HAuCl_4$ also formed appreciable quantities of ethylidene diacetate. The reaction probably proceeds by a mechanism similar to that of the previously studied aromatic substitution reaction. This mechanism involves formation of an intermediate with a palladium(II)–carbon bond. This intermediate reacts with the oxidant to give the observed products.

In the absence of other oxidants palladium(II) salts in acetic acid oxidize ethylene to vinyl acetate[3] and other olefins to mixtures of vinyl and allylic acetates.[4] A study of the product distributions obtained from oxidation of 1 and 2 olefins with palladium(II) acetate

$$C_2H_4 + Pd^{2+} + 2OAc^- \xrightarrow{HOAc} C_2H_3OAc + HOAc + Pd^0 \quad (1)$$

$$Pd(OAc)_2 + C_2H_4 \longrightarrow \underset{\mathbf{1}}{AcOPdCH_2CH_2OAc} \xrightarrow{-HPdOAc} CH_2{=}CHOAc \quad (2)$$

indicated that the reaction proceeds by way of an acetoxypalladation–Pd(II)–hydride elimination.[5]

Addition of copper(II) chloride to these reaction mixtures causes the rate of olefin oxidation to increase. In addition the main product changes from vinyl acetate to 1,2-disubstituted alkanes.[6] It has been demonstrated that both $PdCl_2$ and $CuCl_2$ are required for this reaction

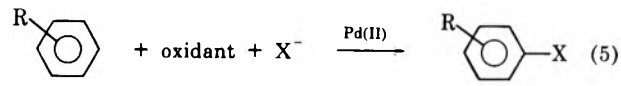
$$C_2H_4 + CuCl_2 + OAc^- \xrightarrow[HOAc + H_2O]{PdCl_2} \begin{cases} AcOCH_2CH_2Cl \\ AcOCH_2CH_2OAc \\ AcOCH_2CH_2OH \end{cases} + CuCl \quad (3)$$

to take place.[6b] On the basis of studies with the butenes[6b] and cyclohexene[1] the mechanism for this reaction has been postulated to involve the interception of the acetoxypalladation intermediate, **1**, by oxidant to give saturated products (X = OAc, Cl, or OH).

$$\mathbf{1} + 2CuCl_2 + X^- \longrightarrow AcOCH_2CH_2X + PdCl_2 + 2CuCl + OAc^- \quad (4)$$

The reaction is not limited to $CuCl_2$, as it has been demonstrated that nitrate can replace $CuCl_2$.[7] The present study is aimed at defining the scope of this new reaction. In particular a number of oxidants will be surveyed to determine what types of oxidants are effective in interacting with Pd(II).

A related reaction is the Pd(II)-catalyzed aromatic substitution reaction, which also requires a second oxidant[8] (X^- = OAc^-, N_3^-, Cl^-, NO_2^-, Br^-, CN^-, or SCN^-).



(5)

This reaction very likely proceeds by way of a Pd(II)–aryl intermediate analogous to **1** although Pd(IV) species cannot be eliminated by the experimental evidence.

Results

A number of oxidants were tested for their ability to change the nature of the oxidation of olefins in the same fashion as $CuCl_2$ or nitrate. In the present work ethylene was the olefin used. There are two criteria for a given reagent to be capable of interacting with Pd(II): first, the rate of ethylene oxidation in the presence of this reagent and Pd(II) as compared to the rate of oxidation in the absence of Pd(II); and second, the product distributions obtained in the oxidations containing Pd(II) and the reagent. Of course, Pd(II) alone gives only vinyl acetate.

Gas Uptake Experiments.—In Table I are listed the results of a series of experiments in which the $Pd(OAc)_2$

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(4) (a) M. N. Vargaftik, I. I. Moiseev, and Ya. K. Sirkin, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 930 (1962); (b) I. I. Moiseev, A. P. Belov, and Ya. K. Sirkin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1527 (1963).

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(8) P. M. Henry, *J. Org. Chem.*, **36**, 1886 (1971).

TABLE I

EFFECT OF VARIOUS OXIDANTS ON THE RATE OF ETHYLENE UPTAKE BY $Pd(OAc)_2$ SOLUTIONS IN ACETIC ACID AT 25° AND ATMOSPHERIC PRESSURE[a]

Oxidant	Initial rate, M hr^{-1}
None	0.017
p-Quinone[b]	0.015
$Pb(OAc)_4$	0.09
$CuBr_2$	0.047
MnO_2	2.0[c]
$FeCl_3$	<0.001
$Fe(OAc)_3$	<0.001
$Hg(OAc)_2$	Very fast[d]
$K_2Cr_2O_7$	0.73
$KMnO_4$	0.004
$NaNO_3$	0.1
$NaNO_2$	0.011
$MoCl_5$	0.005
$MoOCl_4$	0.005

[a] For all solutions $[Pd(OAc)_2]$ = 0.04 M and [LiOAc] = 1 M; concentration of oxidant is also 1 M. Most reaction mixtures were heterogeneous. [b] Concentration of this oxidant is 0.25 M. [c] After ethylene uptake reached 0.04 M the uptake stopped. [d] Gas uptake mass transfer controlled. Uptake stopped after 1 M ethylene concentration was reached.

and LiOAc concentrations are kept constant but contain various oxidants at a concentration of 1 M.

The initial ethylene uptake as measured by gas burets is given for all oxidants. The initial rate is used since in almost all cases the rate of ethylene uptake decreases rapidly with time. For all the oxidants listed in Table I the initial ethylene uptake in the absence of palladium(II) acetate was less than 0.005 M hr^{-1}.

In some cases the oxidant in the absence of $Pd(OAc)_2$ oxidized ethylene at an appreciable rate under the reaction conditions. Three such oxidants are $Tl(OAc)_3$, $TlCl_3$, and $HAuCl_4$. The initial rates of oxidation and product distributions in the presence and absence of $Pd(OAc)_2$ are given in Table II.

Product Distributions.—The reactions listed in Table I were allowed to run under atmospheric ethylene pressure at 25° for 24 hr and then analyzed for the type of products found in the $CuCl_2$-promoted reaction. Results are listed in Table III. Because of the inaccuracy in refilling the gas burets, the total ethylene uptake was not measured. Thus yields could not be calculated, so total concentrations of products are given. For two-electron oxidants such as $Pb(OAc)_4$, the maximum total concentration of oxidation products would be 1 M, and for one-electron oxidations, it would be 0.5 M. For oxidants such as $K_2Cr_2O_7$, which have lower oxidizing states, the maximum expected concentration of products is uncertain. In the case of $CuBr_2$ the main product (*ca.* 0.5 M) was 2-bromoethyl acetate, the product expected by analogy with the reaction of $CuCl_2$ and $PdCl_2$.

Two oxidants, p-quinone and $FeCl_3$, which did not give the promoted oxidation at 25° and atmospheric pressure, were tested under more vigorous conditions. The $FeCl_3$ run was carried out at 100° under an ethylene pressure of 500 psig for 24 hr. Only traces (0.015 M) of vinyl acetate were found in the reaction mixture.

The p-quinone run was carried out under the conditions described in a patent[9] claiming to produce saturated esters. These include 0.007 M $PdCl_2$, 2 M p-quinone, 1.4 M LiCl, and 0.1 M LiOAc. The reaction was run at 69° under 300 psig ethylene pressure for 12 hr. Only vinyl acetate was detected in the reaction mixture.

A control run was carried out to determine if the ethylidene diacetate in the $Tl(OAc)_3$ run could result from further reaction of vinyl acetate. The reaction was carried out in the same fashion as the first run in Table II except that the reaction mixture was initially 0.1 M in vinyl acetate. At the conclusion of the run the reaction mixture still contained 0.1 M vinyl acetate.

(9) H. B. Copelin and M. J. Freamo, Canadian Patent 761,018 (1967).

Discussion

The most important result of the present study is the demonstration that oxidants other than $CuCl_2$ and nitrate will act as cocatalyst with Pd(II) in the oxidation of olefins. On the basis of oxidation rates for the oxidants listed in Table I, $K_2Cr_2O_7$, $Pb(OAc)_4$, $CuBr_2$, $NaNO_2$, and $NaNO_3$, included for purposes of comparison, definitely give the reaction. MnO_2 gave a rapid initial rate but is a doubtful case because the total ethylene uptake was 1 mmol. The data in Table II indicate that $Tl(OAc)_3$, $TlCl_3$, and $AuCl_4^-$ also give the reaction, although the result is obscured by the fact that they oxidize ethylene in the absence of $Pd(OAc)_2$. However, rates are faster in the presence of $Pd(OAc)_2$, and product distributions are different than in its absence.

A number of oxidants, including p-quinone, $FeCl_3$, $Fe(OAc)_3$, $NaNO_2$, $MoCl_5$, $KMnO_4$, and $MoOCl_4$, gave initial rates slower than the rates with $Pd(OAc)_2$ alone, so by this criterion are not effective. $Hg(OAc)_2$ gave a rapid ethylene uptake, but no oxidation resulted. The only reaction was the well-known mercuration reaction.[10]

$$Hg(OAc)_2 + C_2H_4 \xrightarrow{HOAc} AcOHgCH_2CH_2OAc \qquad (6)$$

The product distribution data, samples of which are given in Tables II and III, tend to confirm the ethylene uptake results, since the active cocatalysts gave saturated products. In addition, $NaNO_2$ and $KMnO_4$, which gave a slow ethylene uptake, produced detectable amounts of saturated products. The other oxidants, which gave slow initial rates, also gave no detectable amounts of saturated products. The case of quinone is worthy of special mention because it has been used as a reoxidant for Pd(0) in kinetic studies of olefin oxidation at temperatures close to room temperature.[11] The present results confirm that quinone is suitable for this purpose, since it does not change either the rate or product of the oxidation.

The fact that an oxidant gives little or no activity under the reaction conditions used in this study does not eliminate it as a candidate under more vigorous conditions. Thus $KMnO_4$ gives the aromatic substitution reaction at 90° and almost certainly would give appreciable rates of ethylene oxidation at this temperature. Its slow activity at 25° probably results from low solubility. For this reason two oxidants which gave negative results and are of special interest in Pd(II) chemistry were tested under more vigorous conditions. $FeCl_3$, used as reoxidant for Pd(II) in several patents, still

(10) J. Chatt, *Chem. Rev.*, **48**, 7 (1951).

(11) I. I. Moiseev, A. P. Belov, V. A. Igoshin, and Ya. K. Sirkin, *Dokl. Akad. Nauk SSSR*, **173**, 863 (1967).

TABLE II

INITIAL RATES AND PRODUCT DISTRIBUTIONS WITH $TlCl_3$, $Tl(OAc)_3$, AND $HAuCl_4$ IN THE PRESENCE AND ABSENCE OF $Pd(OAc)_2$[a]

	Reaction Mixtures							
$[Pd(OAc)_2]$, M	0.04		0.04		0.04		0.04	
[LiOAc], M	1.0	1.0			1.0	1.0	1.0	1.0
[NaOAc], M			0.1	0.1				
Oxidant	$Tl(OAc)_3$	$Tl(OAc)_3$	$Tl(OAc)_3$	$Tl(OAc)_3$	$TlCl_3$	$TlCl_3$	$HAuCl_4$	$HAuCl_4$
Concentration of oxidant, M	1.0	1.0	0.4	0.4	1.0	1.0	1.0	1.0
	Initial Rate, M hr^{-1}							
	0.1	0.026	0.103	0.019	0.15	0.0094	0.07	0.011
	Product Distribution, M[b]							
Vinyl acetate	0.006	ND	ND	ND	0.012	ND	0.027	ND
2-Chloroethyl acetate	ND	ND	ND	ND	0.0025	0.013	0.08	0.01
Ethylidene diacetate	0.14	ND	0.2	ND	0.105	ND	0.07	ND
Ethylene glycol diacetate	0.145	0.057	0.082	0.051	0.004	0.033	0.08	0.02
2-Hydroxyethyl acetate	0.023	0.075	0.067	0.045	ND	0.03	ND	0.02

[a] All reactions run for 24 hr before product analysis. [b] ND = not detected (<0.001 M).

TABLE III

PRODUCT DISTRIBUTIONS FOR THE OXIDATION OF ETHYLENE BY $Pd(OAc)_2$ IN THE PRESENCE OF OTHER OXIDANTS[a]

Oxidant	$Pb(OAc)_4$	p-Quinone	MnO_2	$KMnO_4$	$K_2Cr_2O_7$	$NaNO_3$	$NaNO_2$
Vinyl acetate	0.003	0.03	ND[b]	0.004	0.017	ND	ND
Ethylidene diacetate	ND	ND	ND	ND	0.031	0.0017	0.011
Ethylene glycol diacetate	0.08	ND	0.029	0.017	0.43	0.013	0.0031
2-Hydroxyethyl acetate	0.15	ND	ND	ND	0.13	ND	ND
Total	0.233	0.03	0.029	0.021	0.608	0.0147	0.0141

[a] All reaction mixtures 0.04 M in $Pd(OAc)_2$ and 1.0 M in LiOAc. Concentration of oxidant is 1.0 M; reaction run for 24 hr under 1 atm ethylene pressure at 25°. [b] ND = not detected (<0.001 M).

gave no saturated products, and quinone gave only vinyl acetate under conditions previously reported to produce saturated products.[9]

The saturated product distributions deserve comment in some cases. In the case of $CuBr_2$ the main product, as expected in analogy to oxidations by $CuCl_2$, is 2-bromoethyl acetate. The appreciable yields of ethylidene diacetate found with $Tl(OAc)_3$, $TlCl_3$, and $AuCl_4^-$ were not observed with these oxidants in the absence of $Pd(OAc)_2$ or with the other oxidants in the presence of $Pd(OAc)_2$. Control experiments demonstrated that this product was not formed by a secondary reaction of vinyl acetate. Finally, detection of 2-hydroxyethyl acetate in some reaction mixtures was unexpected inasmuch as the reaction mixtures were dried with acetic anhydride, and formation of this acetate would usually require the presence of water. Thus either water is introduced into the reaction in some manner or an intermediate is formed which can react with acetic acid to give this product. An example of the latter could be Cr–O–C bonds in the $K_2Cr_2O_7$ reaction.

The present results do not justify a detailed mechanistic analysis but do emphasize one difference between the aromatic and olefin oxidations previously noted in the study of the aromatic oxidation. This is the fact that the aromatic oxidation requires stronger oxidants than the olefin oxidation. Thus $CuCl_2$ and $Tl(OAc)_3$ give the olefin oxidation but not the aromatic substitution. As mentioned in the introduction, there is good evidence that the $CuCl_2$-promoted oxidation proceeds *via* a Pd(II) species, but there are no definitive experiments to distinguish between mechanisms involving Pd(II) and Pd(IV) species in the case of aromatic substitution. Likewise, the ethylene oxidation with stronger oxidants may proceed through Pd(IV) species. Certainly more mechanistic work is required on both oxidations to distinguish between the two possibilities. Any mechanism will have to explain the formation of ethylidene diacetate in some oxidations.

The properties which cause an oxidant to be a cocatalyst with Pd(II) are certainly not well defined by this study. In general the oxidants with higher redox potentials in aqueous solution appear to give the oxidation, but $CuCl_2$ is certainly an exception with a potential in the range of Fe(III), Mo(VI), and p-quinone. Other factors, such as solubility, may be important. The fact that MnO_2 oxidized only 1 mmol of ethylene may mean that an impurity is the actual active reagent.

Experimental Section

Reagents.—Palladium(II) chloride was purchased from Engelhardt Industries Inc. The thallic acetate was prepared as described earlier.[12] The p-quinone (Aldrich) was recrystallized from ethanol before use. The acetic acid was dried by refluxing over $B(OAc)_3$.[13] Water content was less than 0.01% as determined by Karl Fischer. The lead tetraacetate was purchased from K & K Laboratories, Inc. All other chemicals were of reagent grade.

Experimental Procedure.—All runs at 25° and atmospheric pressure were carried out on a 25-ml scale using creased flasks. The gas uptake was measured by gas burets. The procedure has been described previously.[14] The various reagents were mixed and diluted to 25 ml with acid. Then 0.3 ml of acetic

(12) P. M. Henry, *J. Amer. Chem. Soc.*, **88**, 1597 (1966).
(13) W. C. Eichelberger and V. K. La Mer, *ibid.*, **55**, 3633 (1933).
(14) P. M. Henry, *ibid.*, **86**, 3246 (1964).

anhydride was added and the reaction mixture was heated gently on a steam bath. After cooling the reaction mixture was put in a 25° bath for 0.5 hr before the run was begun. Because of limited solubility of reactants in acetic acid almost all reaction mixtures were heterogeneous.

Analysis of Reaction Mixtures.—All analyses were carried out by vapor phase chromatography using a 6-ft column packed with 20% Carbowax 20M on a 70–80 mesh ABS support. The temperature was programmed from 80 to 200° at a rate of 7.5°/min. The helium flow rate was 60 ml/min. Standards of vinyl acetate and all the saturated products were prepared and used to calculate the concentration of the various products.

Registry No.—Ethylene, 74-85-1; $Pd(OAc)_2$, 3375-31-3; $Tl(OAc)_3$, 2570-63-0; $HAuCl_4$, 16903-35-8; $TlCl_3$, 13453-32-2.

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(+)-Limonene Oxidation with Selenium Dioxide–Hydrogen Peroxide

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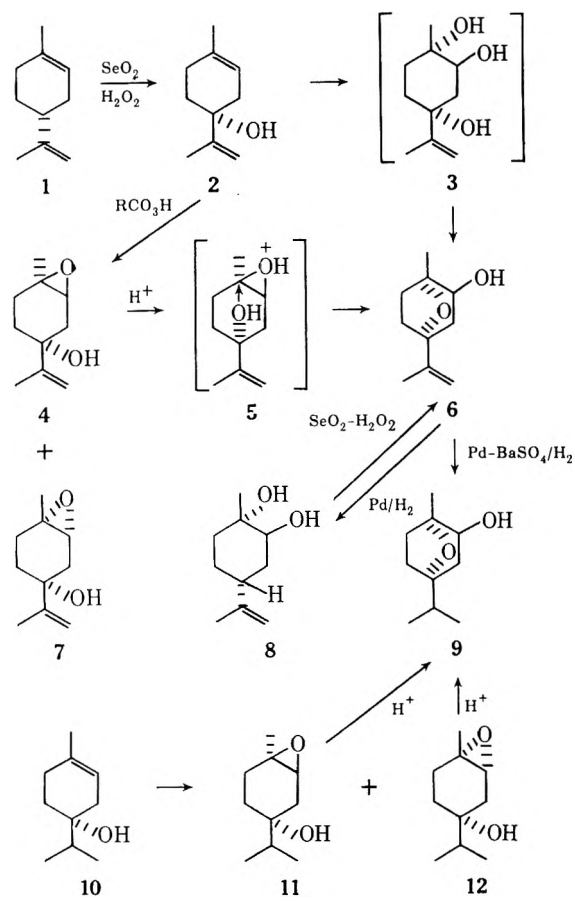
(+)-Limonene oxidation with selenium dioxide–hydrogen peroxide has afforded (+)-1-hydroxyneodihydrocarveol (8) as the main product plus (−)-carvone, (−)-*cis*-carveol, (−)-*trans*-carveol, (−)-1,8-*p*-menthadien-4-ol (2), and three other alcohols. One of the alcohols, (−)-1,4-epoxyneoisodihydrocarveol (6), is a new compound whose structure was determined and whose mechanism for formation was explored. (−)-1,8-*p*-Menthadien-4-ol (2) was oxidized with *m*-chloroperbenzoic acid to produce the previously unreported (−)-4-hydroxy-*trans*-8-*p*-menthene oxide (4), and (−)-4-hydroxy-*cis*-8-*p*-menthene oxide (7). The trans oxide 4, but not the cis isomer 7, was converted to 6 with acetic acid. Terpinen-4-ol (10) was similarly oxidized with peracid, and both the cis and trans isomers (11 and 12) afforded a 1,4-epoxide (9) upon treatment with dilute sulfuric acid.

Selenium dioxide oxidation of (+)-limonene has been studied by several workers,[2a–d] and the products identified involved oxidation at all allylic positions except carbon-3 (menthol series). Most of these oxidation products are constituents of natural products such as citrus essential oils,[2e] of which (+)-limonene is the major constituent. As part of a program to explore conversion of (+)-limonene to more valuable fine chemicals, we studied (+)-limonene oxidation with hydrogen peroxide and only a catalytic amount of selenium dioxide.[3] Among the oxidation products was a new 1,4-epoxide derivative (6 in Scheme I) whose structure was determined and whose mechanism for formation was explored.

Table I lists the products identified from selenium dioxide–hydrogen peroxide oxidation of (+)-limonene under four sets of reaction conditions. Increasing the proportion of oxidizing agents increased the yield of most products (reaction 2). Decreasing the catalytic amount of selenium dioxide (reaction 3) decreased the percentage of all oxidation products except (−)-*cis*-carveol, (+)-1-hydroxyneodihydrocarveol (8), and 1,8-*p*-menthadien-7-ol. Stopping the reaction at the end of the initial exothermic period (reaction 4) resulted in decreased yield of all oxidation products. For most products yield was best with high proportions of oxidizing agents and a long reaction time (reaction 2).

One of the main oxidation products of this reaction is a previously unreported compound, (−)-1,4-epoxyneoisodihydrocarveol[4] (6 in Scheme I). The ir spectrum suggested that this compound contained either

SCHEME I



two hydroxyl groups or one hydroxyl group and an ether linkage [1045 (C–OH), 1118 cm^{-1} (C–O–C or *t*-OH)].[5] A high-resolution mass spectrum showed the empirical formula to be $C_{10}H_{16}O_2$. The low-resolution mass spectrum showed a major fragment due to loss of one water molecule (M − 18), but a second molecule

(1) One of the laboratories of the Southern Region, Agricultural Research Service, U. S. Department of Agriculture. References to specific commercial products do not constitute endorsement.

(2) (a) J. Verghese, *Perfum. Essent. Oil Rec.*, 876 (1968); (b) Y. Sakuda, *Bull. Chem. Soc. Jap.*, **42**, 3348 (1969); (c) A. F. Thomas and W. Bucher, *Helv. Chim. Acta*, **53**, 770 (1970); (d) E. N. Trachtenberg and J. R. Carver, *J. Org. Chem.*, **35**, 1646 (1970); (e) G. L. K. Hunter and M. G. Moshonas, *J. Food Sci.*, **31**, 167 (1966).

(3) M. Fieser and L. Fieser, "Reagents for Organic Synthesis," Vol. 2, Wiley, New York, N. Y., 1969, p 362.

(4) See E. E. Royals and J. C. Leffingwell, *J. Org. Chem.*, **31**, 1937 (1966), for nomenclature.

(5) R. N. Jones, "National Research Council Bulletin," No. 6, Ottawa, Canada.

Table I

Products from d-Limonene Oxidation with SeO_2–H_2O_2

	Compd	Glc peak area % 1[a]	2[b]	3[c]	4[d]
1	(+)-Limonene	68.7	47.1	74.6	92.4
2	(−)-Carvone	1.4	3.7	0.8	0.2
3	(−)-*trans*-Carveol	4.2	3.1	1.9	0.4
4	(−)-*cis*-Carveol	0.9	2.0	0.9	0.2
5	(−)-1,4-Epoxyneoisodihydrocarveol (6)	1.8	4.5	0.8	0.2
6	(+)-1-Hydroxyneodihydrocarveol (8)	10.2	22.1	13.7	4.2
7	(−)-1,8-*p*-Menthadien-4-ol (2)	6.2	9.3	2.7	0.8
8	1,8-*p*-Menthadien-7-ol	0.8	2.6	1.1	0.3
9	1,8-*p*-Menthadien-10-ol	4.5	3.2	2.7	0.5
10	α,*p*-Dimethylstyrene	Tr	0.2	0.5	0.2
11	Hydrocarbon (unidentified)	0.9	1.7	0.5	0.2

[a] Reaction conditions: 32 mmol SeO_2, 0.66 mol H_2O_2, 0.6 mol (+)-limonene, 4 hr. [b] 32 mmol SeO_2, 0.66 mol H_2O_2, 0.3 mol (+)-limonene, 4 hr. [c] 16 mmol SeO_2, 0.66 mol H_2O_2, 0.6 mol (+)-limonene, 4 hr. [d] 32 mmol SeO_2, 0.66 mol H_2O_2, 0.6 mol (+)-limonene, 20 min.

of water was not lost as is the case with the 1,2 diol **8**.[6] The nmr spectrum in dimethyl sulfoxide-d_6 showed two methyl singlets at δ 1.30 and 1.70 ppm assigned to the tertiary methyl and terminal allylic methyl groups, respectively, a one-proton multiplet centered at 3.5 ppm assigned to the carbon at position 2 bearing the hydroxyl group, and two one-proton singlets at 4.70 and 4.85 ppm asigned to the vinyl hydrogens on the terminal double bond. The hydroxyl hydrogen appeared as a one-proton doublet at 4.99 ppm. Upon addition of a trace of sulfuric acid, this doublet collapsed to a singlet appearing at 5.8 ppm.[7] Reduction of **6** with hydrogen and a 10% palladium on carbon catalyst afforded **8**, formed by hydrogenolysis of the allylic carbon–oxygen bond at C-4. Surprisingly, the double bond was not reduced under these conditions. Reduction of **6** with hydrogen and 5% palladium on barium sulfate afforded the known saturated derivative 1,4-epoxyneoisocarvomenthol (**9**), which was also prepared from terpinen-4-ol (**10**) by a procedure similar to that previously described.[8]

Possible pathways for formation of **6** from (+)-limonene have been explored. The main product of selenium dioxide–hydrogen peroxide oxidation of (+)-limonene, (+)-1-hydroxyneodihydrocarveol (**8**), was oxidized to **6** under the same conditions used to obtain **6** from (+)-limonene. An intermediate, 1,4-dihydroxyneoisodihydrocarveol (**3**), probably formed in this reaction, can then be dehydrated to **6** just as in the formation of 1,4-cineole from 1,4-dihydroxy-*p*-menthane.[9] Chromium trioxide–pyridine oxidation of **8** also afforded **6**.

An alternate pathway for formation of **6** from (+)-limonene involves initial oxidation at C-4 to afford 1,8-*p*-menthadien-4-ol (**2**). Treatment of **2** with selenium dioxide and hydrogen peroxide did yield **6** in addition to the major product α,*p*-dimethylstyrene. Since selenium dioxide–hydrogen peroxide can oxidize an olefin to the corresponding 1,2 diol,[10] **3** is a possible intermediate in the formation of **6** from **2**. An intermediate 1,2 epoxide has been implicated in 1,2-diol formation from an olefin in this oxidation reaction.[10] Thus, **6** also can be obtained from **2** through a 1,2-epoxy-4-ol, *e.g.*, **4**.

Limonene 1,2-epoxide (1:1 mixture of cis and trans isomers)[11] is another possible intermediate in the oxidation of limonene to 1,4 epoxide **6**. Treatment of limonene 1,2-epoxide with selenium dioxide–hydrogen peroxide afforded **6** in small yield with **8** being the major product. In the conversion of limonene 1,2-epoxide to **6**, 4-hydroxy-8-*p*-menthene oxide is a likely intermediate. We prepared the previously unreported cis and trans isomers, **7** and **4**, respectively, of this suggested intermediate by epoxidation of the endocyclic double bond in **2** with peracid. The trans isomer **4** was readily converted to **6** upon treatment with acetic acid, but the cis isomer **7** decomposed under the same conditions and no starting material or **6** could be separated from the reaction mixture by gc. A concerted acid-catalyzed 1,2-epoxide opening and 1,4-epoxide formation, as illustrated in intermediate **5**, is sterically favorable in the trans isomer (**4**), but not in the cis isomer (**7**). If the peracid oxidation of **2** was allowed to stand for a longer time, only cis isomer **7** and 1,4 epoxide **6** were isolated, apparently because enough acid was present in the reaction mixture to convert the trans epoxide to **6**. Structures of **4** and **7** were assigned on the basis of the conversion of **4** to 1,4 epoxide **6**, on the relative gc retention times as compared to the saturated analogs,[12] and on the fact that the cis isomer **7** was reduced with palladium and hydrogen to 4-hydroxycarvomenthol.[12]

Of the three discussed pathways for formation of **6** from (+)-limonene, that involving initial oxidation to **8** seems the most probable. Thus, **8** is the major reaction product in all cases in Table I. The ratio of a secondary reaction product to a primary product should increase with time, and in (+)-limonene oxidation the ratio of secondary product **6** to primary product **8** shows a greater increase with time (**6**:**8** = 0.05 in run 4 and 0.18 in run 1 of Table I) than does that of **6** to primary product **2** (**6**:**2** = 0.25 in run 4 and 0.30 in run 1). Limonene 1,2-epoxide is the least likely intermediate considered because none was found among the products even under the shortest reaction time used (run 4); epoxidation of olefins with selenium dioxide and hydrogen peroxide has been reported, however.[13]

Oxidation of (+)-limonene to (−)-carvone and (−)-*cis*- and (−)-*trans*-carveols in this study indicates attack primarily at the 1,2 double bond[4] rather than allylic oxidation at C-6[14] to form these oxidation products. The (−)-*cis*- and (−)-*trans*-carveols are probably not intermediates in (−)-carvone formation, since the latter is of higher optical purity. Furthermore, the ratio of carvone to carveols does not increase with time (carvone:carveols = 0.33 in run 4 and 0.28

(6) G. L. K. Hunter and M. G. Moshonas, *Anal. Chem.*, **37**, 378 (1965).
(7) O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, **86**, 1256 (1964).
(8) P. Garside, T. G. Halsall, and G. M. Hornby, *J. Chem. Soc. C*, 716 (1969).
(9) J. L. Simonsen, "The Terpenes," Vol. 1, University Press, Cambridge, England, 1953, p 304.
(10) W. Sonoda and S. Tsutsumi, *Bull. Chem. Soc. Jap.*, **38**, 958 (1965).
(11) See Royals and Leffingwell,[4] footnote 49.
(12) G. Ohloff and G. Uhde, *Helv. Chim. Acta*, **48**,10 (1965).
(13) J. Itakura, H. Tanaka, H. Ito, and T. Matsubara, Japanese Patent 19,894 (1970); *Chem. Abstr.*, **73**, 109375*j* (1970).
(14) A. Blumann and O. Zeitschel, *Chem. Ber.*, **46**, 1178 (1913); H. E. Eschnazi, *Israel Res. Council Bull.*,109 (1951).

in run 1 of Table I) as should be the case if the carveols were intermediates in carvone formation.

A comparison sample of 1,4-epoxyneoisocarvomenthol (**9**) was prepared by epoxidation of terpinen-4-ol (**10**) to 4-hydroxy-*trans*-carvomenthane epoxide (**11**) and 4-hydroxy-*cis*-carvomenthane epoxide (**12**) followed by acid-catalyzed epoxide opening of either **11** or **12** to **9**. Garside, *et al.*,[8] who prepared **9** from **10** by peracid oxidation, had proposed **11** as an intermediate in their reaction, but had not isolated it. We epoxidized **10** with *m*-chloroperbenzoic acid and isolated **11** and **12**,[12] both of which rearranged to **9** upon treatment with 0.1 *N* sulfuric acid. However, only the trans isomer (**11**) cleanly afforded **9**, while the cis isomer (**12**) also produced significant quantities of *p*-cymene and carvenone. The structures of **11** and **12** were confirmed by lithium aluminum hydride reduction of **11** to *trans*-*p*-menthane-1,4-diol as previously reported,[12] and the cis epoxide to 4-hydroxycarvomenthol[12] plus a small amount of *cis*-*p*-menthane-1,4-diol. The 4-hydroxycarvomenthol, thus prepared, was identical with that obtained by catalytic reduction of **7** described above.

Absolute configurations of the compounds, as shown in Scheme I, were determined by comparison of **8** and terpinen-4-ol (**10**) isolated in this study with previously reported samples of known configuration. Compound **8**, having mp 66.5–67.5° and $[\alpha]D$ +41°, was the isomer previously obtained from peracid oxidation of (+)-limonene and has the 1*S*,2*S*,4*R* configuration.[15] Catalytic reduction of 1,8-*p*-menthadien-4-ol (**2**) afforded (4*R*)-terpinen-4-ol with $[\alpha]D$ −36° of established configuration (reported $[\alpha]D$ −34°).[12] The 1,8-*p*-menthadien-4-ol (**2**) obtained from this selenium dioxide and hydrogen peroxide oxidation reaction had $[\alpha]D$ −43°, whereas the 1,8-*p*-menthadien-4-ol obtained previously from selenium dioxide oxidation of (+)-limonene either was optically inactive[2b,c] or slightly dextrorotatory.[2d] Presently accepted mechanisms for selenium dioxide oxidation of olefins to allylic alcohols[16] do not explain this formation of optically active 1,8-*p*-menthadien-4-ol (**2**) from (+)-limonene, because the proposed intermediate contains a 4,8 double bond, and should be attacked equally from either side of the molecule at C-4 to produce racemic 1,8-*p*-menthadien-4-ol.[2c] In the present case, stereospecific hydrogen removal and oxygen addition with inversion at C-4 must take place without racemization.

Experimental Section

Infrared spectra were obtained on thin liquid films with a Perkin-Elmer Infracord. Nuclear magnetic resonance spectra were obtained with a Varian A-60 spectrometer on samples dissolved in deuteriochloroform or dimethyl-d_6 sulfoxide containing tetramethylsilane as internal standard. Optical rotations were determined on absolute ethanol solutions with a Rudolph Model 62 polarimeter. Low-resolution mass spectra were determined at 70 eV with a Bendix Model 3012 Time-of-Flight mass spectrometer, and high-resolution mass spectra with an A. E. I. Picker ultrahigh-resolution mass spectrometer. Melting points were determined between glass plates on a Nalge block type melting point apparatus and are uncorrected.

Gas chromatographic analyses and separations were performed on F & M Model 500 and 700 gas chromatographs equipped with 0.20 in. i.d. × 20 ft stainless steel columns packed with 20% Carbowax 20M on 60/80 mesh Gas-Chrom P and using thermal conductivity detectors. Temperature programming was from 100 to 220° at 1°/min at a He flow rate of 100 ml/min and an injection port temperature of 245°. Peak areas were determined as height times width at half-height. When reaction product percentages are listed, they were determined by integrating the gc curve for the crude reaction mixture.

(+)-Limonene was obtained from distillation of Valencia orange essence oil,[17] bp 45–50° (1.5 mm), $[\alpha]^{29}D$ +116.5° (*c* 1.24), and was shown to be greater than 99% pure by gc.

Selenium Dioxide–Hydrogen Peroxide Oxidation of (+)-Limonene.—Selenium dioxide (3.6 g, 32.4 mmol) and 75 g (0.66 mol) of 30% hydrogen peroxide were added to a stirred solution of 80 g (0.6 mol) of (+)-limonene in 100 ml of tetrahydrofuran (THF). The mixture was heated until a vigorous exothermic reaction ensued. After 10 min, the exothermic reaction began to subside and the mixture was heated to reflux. Three separate oxidations (see footnotes to Table I), varying the molar quantities of reagents, were conducted in this manner. A fourth reaction was also carried out in which the initial exothermic reaction was allowed to subside (20 min) and the mixture was not heated further.

In each case, the reaction products were isolated by removing the THF solvent at 30° and water pump pressure on a rotary evaporator (Buchi Rotavapor R, Type KRV 65/45) and the bulk of the (+)-limonene was then removed in the same apparatus at 40° and 1 mm pressure. Portions of the residual liquid were subjected to gc to separate individual products for identification. Carvone, $[\alpha]^{29}D$ −54.5° (*c* 0.67), *cis*-carveol, $[\alpha]^{29}D$ −12.8° (*c* 1.56), *trans*-carveol, $[\alpha]^{29}D$ −90° (*c* 1.11), 1,8-*p*-menthadien-10-ol, and 1-hydroxyneodihydrocarveol [mp 66.5–67.5° and $[\alpha]^{29}D$ +41.0° (*c* 1.86) after two crystallizations of a gc-purified sample from benzene–hexane[15b]] were all identified by comparison of their infrared spectra with those from authentic samples obtained previously at our laboratories.[2,17] Authentic samples of α,*p*-dimethylstyrene and 1,8-*p*-menthadien-7-ol were obtained from commercial sources. Quantitative estimates as listed in Table I have been corrected to include the limonene removed by distillation.

The ir, nmr, and mass spectra of 1,8-*p*-menthadien-4-ol (**2**) were identical with those already reported.[18] Both compounds **2** and **6** could be isolated in >90% purity by distillation of the residue after removing the bulk of the (+)-limonene: (−)-1,8-*p*-menthadien-4-ol (**2**), bp 34–36° (0.1 mm), gc purified sample showed $[\alpha]^{29}D$ −43.0° (*c* 1.24); (−)-1,4-epoxyneoisodihydrocarveol (**6**), bp 58–65° (0.1 mm), gc-purified sample showed $[\alpha]^{29}D$ −89.2° (*c* 1.35); ir 3490 (s), 2995 (s), 1650 (s), 1450 (s), 1380 (s), 1320 (w), 1270 (w), 1235 (w), 1220 (sh), 1200 (w), 1180 (w), 1118 (s), 1100 (sh), 1045 (s), 1035 (sh), 1010 (w), 985–975 (m, split), 950 (m), 900 (m), 875 (m), 815 (w), 755 cm^{-1} (w); mass spectrum *m/e* (rel intensity) 168 (9), 150 (14), 124 (11), 107 (26), 97 (11), 95 (20), 92 (14), 84 (20), 82 (12), 81 (13), 69 (30), 67 (11), 58 (13), 55 (16), 43 (100), 41 (40); high resolution *m/e* 168.1148 (calcd for $C_{10}H_{16}O_2$, 168.1149); nmr (Me_2SO-d_6) δ 1.30 (s, 3, *t*-CH_3), 1.70 (s, 3, =CCH_3), 3.50 (m, 1, CHOR), 4.70 and 4.85 (s, 2, C=CH_2), 4.99 (d, 1, J = 4 Hz, OH); the latter, with a trace H_2SO_4 added, shifted to δ 5.87 (s).[7] The monoacetate derivative of **6** was prepared with acetic anhydride and pyridine: ir 1730, 1240 cm^{-1} (-$COOCH_3$); mass spectrum *m/e* (rel intensity) 210 (3), 168 (3), 151 (9), 150 (8), 135 (6), 107 (10), 92 (8), 84 (8), 69 (17), 58 (3), 55 (7), 43 (100).

Oxidation of Limonene 1,2-Epoxide to 6.—To 80 g (0.52 mol) of limonene 1,2-epoxide[11] (FMC Corp., New York, N. Y.) in 100 ml of THF were added 0.66 mol of 30% hydrogen peroxide and 32 mmol of selenium dioxide following the above procedure (4-hr reflux) for (+)-limonene oxidation. Gc separation of the crude reaction mixture after removal of solvent afforded limonene 1,2-epoxide (6%), 1,4-epoxyneoisodihydrocarveol (**6**) (8%), and 1-hydroxyneodihydrocarveol (**8**) (86%) based on relative gc peak areas.

Oxidation of 1,8-*p*-Menthadien-4-ol (2) to 6.—To 0.90 g (6.0 mmol) of **2** in 50 ml of THF were added 4.0 mmol of 30% hydro-

(15) (a) H. Schmidt, *Chem. Ber.*, **82**, 11 (1949); (b) W. F. Newhall, *J. Org. Chem.*, **29**, 185 (1964).

(16) J. P. Schaefer, B. Horvath, and H. P. Klein, *J. Org. Chem.*, **33**, 2647 (1968); E. N. Trachtenberg, C. H. Nelson, and J. R. Carver, *ibid.*, **35**, 1653 (1970); K. B. Sharpless and R. F. Lauer, *J. Amer. Chem. Soc.*, **94**, 7154 (1972).

(17) R. L. Coleman and P. E. Shaw, *J. Agr. Food Chem.*, **19**, 520 (1971).

(18) H. E. Eschinasi, *Israel J. Chem.*, **6**, 713 (1968); T. Sakai, K. Yoshihara, and Y. Hirose, *Bull. Chem. Soc. Jap.*, **41**, 1945 (1968); S. Kusumoto, A. Ohsuka, and M. Kotake, *ibid.*, **41**, 1950 (1968).

gen peroxide and 2.7 mmol of selenium dioxide following the above procedure for (+)-limonene oxidation. Gc separation of the crude reaction mixture after removal of solvent yielded 7% *p*-cymene, 56% α,*p*-dimethylstyrene, 17% starting material (**2**), and 20% 1,4-epoxyneoisodihydrocarveol (**6**).

Oxidation of (+)-1-Hydroxyneodihydrocarveol (8) to (−)-1,4-Epoxyneoisodihydrocarveol (6). A. With Selenium Dioxide–Hydrogen Peroxide.—To 3.0 g (17.4 mmol) of **8** in 50 ml of methylene chloride were added 8.0 mmol of 30% hydrogen peroxide and 1.4 mmol of selenium dioxide following the procedure for (+)-limonene oxidation. Gc separation of the crude reaction mixture after separation of the layers and removal of methylene chloride afforded a 9:1 mixture of starting material **8** and (−)-1,4-epoxyneoisodihydrocarveol (**6**), $[\alpha]^{29}D$ −91.8° (*c* 0.98).

B. With Chromium Trioxide–Pyridine.—To 20 mg of **8** in 25 μl of pyridine was added 500 μl of a 10% solution of the CrO_3–pyridine complex[19] in methylene chloride, and the reaction mixture was kept for 18 hr at room temperature. The solution was decanted from a brown precipitate that had formed during the reaction, the solvent was removed under N_2 at 35°, and the residue was separated by gc to afford a 2:3 mixture of **6** and starting material **8**.

Peracid Oxidation of 1,8-*p*-Menthadien-4-ol (2).—To 0.8 g (5.2 mmol) of **2** in 10 ml of methylene chloride cooled in an ice bath were added 0.9 g (5.2 mmol) of *m*-chloroperbenzoic acid (K & K Laboratories, Inc., Plainview, N. Y.) in 10 ml of methylene chloride followed by 25 ml of saturated aqueous sodium carbonate solution. The reaction mixture was kept in the ice bath and stirred for 4 hr, the layers were separated, and the organic layer was concentrated under N_2. Separation of the residue by gc afforded 12% starting material (**2**) and 67% (−)-4-hydroxy-*cis*-8-*p*-menthene oxide (**7**): $[\alpha]^{29}D$ −81.2° (c 1.23); ir 3600 (s), 3050 (s), 1655 (m), 1450 (s), 1420 (w), 1380 (m), 1360 (w), 1340 (m), 1305 (w), 1265 (w), 1240 (m), 1225 (w), 1215 (w), 1200 (w), 1140 (w), 1130 (w), 1115 (m), 1095 (m), 1090 (m), 1085 (m), 1060 (s), 1135 (m), 1120 (m), 1005 (w), 985 (m), 970 (w), 905 (s), 855 (s), 840 (s), 775 cm^{-1} (s); mass spectrum *m/e* (rel intensity) 168 (21), 107 (10), 97 (11), 95 (11), 84 (29), 83 (19), 82 (7), 81 (14), 71 (19), 69 (82), 55 (40), 44 (64), 43 (100), 41 (81); high resolution *m/e* 168.1149 (calcd for $C_{10}H_{16}O_2$, 168.1149); nmr ($CDCl_3$) δ 1.35 (s, 3, *t*-CH_3), 1.78 (s, 3, =CCH_3), 3.2 (m, 1, CHOR), 4.90 and 5.02 (2 singlets, 2, C=CH_2); and 17% (−)-4-hydroxy-*trans*-8-*p*-menthene oxide (**4**): $[\alpha]^{29}D$ −88.4° (*c* 1.13); ir 3450 (s), 2950 (s), 1645 (m), 1440 (s), 1420 (m), 1380 (m), 1360 (m), 1305 (m), 1260 (m), 1230 (w), 1215 (s), 1118 (m), 1090 (m), 1060 (s), 1040 (m), 1018 (m), 1005 (w), 975 (m), 950 (m), 905 (s), 845 (s,) 785 (m), 718 cm^{-1} (m); mass spectrum *m/e* (rel intensity) 168 (2), 153 (2), 150 (3), 110 (9), 107 (14), 97 (8), 95 (12), 84 (16), 83 (11), 82 (12), 81 (9), 71 (11), 69 (26), 67 (12), 58 (11), 55 (20), 53 (9), 44 (19), 43 (100), 41 (49), 39 (28); high resolution *m/e* 168.1143 (calcd for $C_{10}H_{16}O_2$, 168.1149); nmr ($CDCl_3$) δ 1.27 (s, 3, *t*-CH_3), 1.67 (s, 3, =CCH_3), 2.92 (m, 1, CHOR), 4.80 and 4.94 (singlets, 2, C=CH_2).

When the peracid reaction mixture was removed from the ice bath after 4 hr, allowed to stir at room temperature 20 hr longer, and worked up as described above, the products isolated by gc were about equal quantities of **7** and 1,4-epoxyneoisodihydrocarveol (**6**).

Rearrangement of 4-Hydroxy-*trans*-8-*p*-menthene Oxide (4) to 6.—When 4 μl of **4** was treated with 20 μl of 9:1 acetic acid–water and in 5 min injected onto the gc column, a 2:1 mixture of starting material **4** and **6** was obtained. When 4-hydroxy-*cis*-8-*p*-menthene oxide (**7**) was treated under the same conditions, no starting material, or **6**, or other gc-volatile products could be isolated.

Reduction of 1,4-Epoxyneoisodihydrocarveol (6) to 8.—To 50 μl of **6** in 0.5 ml of absolute EtOH was added 50 mg of 10% Pd/C and the mixture was shaken at 50 psi hydrogen for 24 hr in a Parr hydrogenation apparatus. The catalyst was removed by filtration, the filtrate was concentrated to small volume, and the residue was separated by gc to afford **8**, $[\alpha]^{29}D$ +39.5° (*c* 1.32), as the only product isolated, which was identified by ir comparison with an authentic sample.[2e]

Reduction of 7 to 4-Hydroxycarvomenthol.—Catalytic reduction of **7** with 10% Pd/C by the above procedure afforded, by gc separation, 4-hydroxycarvomenthol (identified by ir comparison to the authentic sample prepared below by $LiAlH_4$ reduction of **11**), and *cis*- and *trans*-*p*-menthan-4-ol, which were identified by comparison of their ir spectra to published spectra for these two alcohols.[20]

Reduction of 6 to 1,4-Epoxyneoisocarvomenthol (9).—When hydrogenation of **6** was carried out as described above except that 5% Pd on $BaSO_4$ catalyst was used, the product isolated by gc was identified as **9** by comparison of its ir and mass spectra to those of an authentic sample prepared as described below.

Preparation of (−)-1,4-Epoxyneoisocarvomenthol (9) from Terpinen-4-ol (10).—Epoxidation of **10** with 1 equiv of *m*-chloroperbenzoic acid by the above described procedure for peracid oxidation of **2** afforded, by gc analysis, 26% starting material, 62% 4-hydroxy-*cis*-carvomenthene epoxide (**12**), and 12% 4-hydroxy-*trans*-carvomenthene epoxide (**11**). The relative retention times and mass spectra matched those reported for these two epoxides.[12]

The cis epoxide **12** (shorter gc retention time) was reduced with $LiAlH_4$ as described previously[12] to afford, by gc separation, 4-hydroxycarvomenthol whose mass spectrum was identical with that published for this compound,[12] and a trace of *cis*-*p*-menthane-1,4-diol, mp 116–117.5°, whose ir and mass spectra were identical with those of an authentic sample prepared as described previously from ascaridole.[21] The trans epoxide **11** (longer gc retention time) was reduced with $LiAlH_4$, as described previously, to *trans*-*p*-menthane-1,4-diol,[12] whose ir spectrum was identical with that of a comparison sample prepared below.

The comparison sample was prepared by adding to 0.5 g of **10** a mixture of 1.0 g of $Hg(OAc)_2$ in 30 ml of water and 30 ml of THF, and after 10 min, 30 ml of 3 *N* NaOH and 30 ml of 0.5 *M* $NaBH_4$ in 3 *N* NaOH were added.[22] The reaction mixture was filtered, the filtrate was saturated with NaCl, the layers were separated, the upper organic layer was concentrated to dryness, and the crystalline residue was recrystallized three times from hexane to yield *trans*-*p*-menthane 1,4-diol, mp 135–136.5°.

After treatment of *ca.* 10 μl of 4-hydroxy-*trans*-carvomenthane epoxide (**11**) with 100 μl of THF and 50 μl of 0.1 *N* H_2SO_4 for 5 min and injection of the mixture onto the gc the only product isolated was **9** $[\alpha]^{29}D$ −76.2° (*c* 1.35).[8] Similar treatment of 4-hydroxy-*cis*-carvomenthene epoxide (**12**) afforded a smaller quantity of **9** with significant amounts of *p*-cymene and carvenone also identified. Carvenone was identified by ir comparison with that of an authentic sample,[23] and the *p*-cymene by ir and mass spectral comparison with that of a sample purchased commercially.

Reduction of 1,8-*p*-Menthadien-4-ol (2) to Terpinen-4-ol (10).[24]—A 500-μl sample of **2**, bp 34–36° (0.1 mm), in 1 ml of absolute ethanol was shaken with 10% Pd on carbon under 60 psi hydrogen for 4 hr in a Parr hydrogenation apparatus. The catalyst was allowed to settle and portions of the solution were separated by gc to afford terpinen-4-ol (**10**), $[\alpha]^{29}D$ −36° (*c* 1.44), as the main product with some starting material and *p*-menthan-4-ol also identified.

Registry No.—**1**, 5989-27-5; **2**, 38630-70-5; **4**, 38630-71-6; **6**, 38630-72-7; **6** monoacetate, 38630-73-8; **7**, 38630-74-9; **8**, 38630-75-0; **9**, 38630-76-1; **10**, 20126-76-5; SeO_2, 7446-08-4; H_2O_2, 7722-84-1; (−)-carvone, 6485-40-1; (−)-*cis*-carveol, 2102-59-2; (−)-*trans*-carveol, 2102-58-1; 1,8-*p*-menthadien-10-ol, 3269-90-7.

(19) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

(20) B. M. Mitzner, V. J. Mancini, S. Lemberg, and E. T. Theimer, *Appl. Spectrosc.*, **22**, 34 (1968).

(21) O. Wallach, *Justus Liebigs Ann. Chem.*, **392**, 59 (1912).

(22) H. C. Brown and P. Geoghegan, Jr., *J. Amer. Chem. Soc.*, **89**, 1522 (1967).

(23) Kindly furnished by Dr. Ross Sheldon, Glidden-Durkee Co., Jacksonville, Fla.

(24) J. C. Leffingwell, U. S. Patent 3,609,197 (Sept 28, 1971).

Reaction of 24,28-Epoxides of Sterol Side Chain with Boron Trifluoride Etherate[1]

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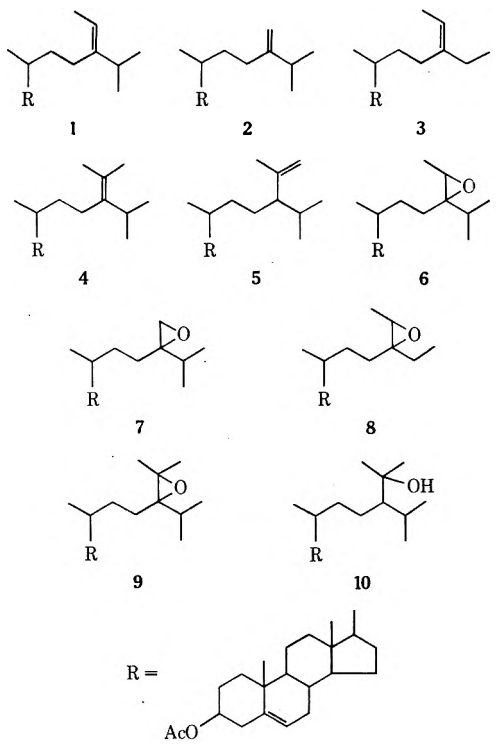
Brief treatment of 24,28-epoxystigmast-5-en-3β-yl acetate (6) with boron trifluoride etherate gave a fragmentation product, desmosteryl acetate (11, 35%), together with 24-acetylcholesteryl acetate (12, 45%) and 24-formyl-24-methylcholesteryl acetate (13, 12%). By contrast, when the analogous epoxides, 24,28-epoxyergost-5-en-3β-yl acetate (7), 24,28-epoxy-26-norstigmast-5-en-3β-yl acetate (8), and 24,28-epoxy-28-methylstigmast-5-en-3β-yl acetate (9) were treated with this reagent, no fragmentation reaction occurred, but 24-formylcholesta-3,5-diene (15, 12%), 24-acetyl-26-norcholesteryl acetate (14, 100%), and 24-acetyl 24-methylcholesteryl acetate (16, 22%) were obtained, respectively. The reactions of epoxide 6 with other Lewis acids and protonic acids are also described.

While the BF_3-catalyzed reaction of epoxides in the steroidal nucleus has been extensively studied,[2] the investigation of side-chain epoxides is relatively limited.[3] In continuation of our studies on the chemical reactivity of the side-chain double bond of fucosteryl acetate (1) (Chart I),[4] we have found a novel

CHART I



fragmentation reaction of 24,28-epoxystigmast-5-en-3β-yl acetate (6) to give desmosteryl acetate (11) by brief treatment with boron trifluoride etherate.[5] A similar reaction seems to occur in insects during the dealkylation of β-sitosterol to cholesterol, from the evidence that tritiated 24,28-epoxystigmast-5-en-3β-ol was shown to be effectively transformed into cholesterol in silkworm.[6]

Details on the reactions of the epoxide will be described in this paper. Furthermore, to test the effect of structural variations of the epoxide on the fragmentation reaction, several analogous epoxides (7, 8, and 9) were prepared and their reaction with boron trifluoride etherate was examined. The influence of various acids on the reaction behavior was also tested.

Results and Discussion

Preparation of Epoxides.—The following epoxides were prepared: 24,28-epoxystigmast-5-en-3β-yl acetate (6), 24,28-epoxyergost-5-en-3β-yl acetate (7), 24,28-epoxy-26-norstigmast-5-en-3β-yl acetate (8), and 24,28-epoxy-28-methylstigmast-5-en-3β-yl acetate (9). 24-Methylenecholesteryl acetate (2) was synthesized by a Wittig reaction of 24-oxocholeteryl acetate,[7] prepared from fucosteryl acetate by ozonolysis. Similarly 26-norfucosteryl acetate (3) was obtained in 20% yield from 24-oxo-26-norcholesteryl acetate[4] by a Wittig reaction with ethylenetriphenylphosphorane. Treatment of 1, 2, or 3 with 1 equiv of *m*-chloroperbenzoic acid afforded the corresponding epoxides, 6, 7, and 8 in the yield of 75, 18, and 73%, respectively.

The attempted preparation of 24-isopropylidenecholesteryl acetate (4) by a Wittig reaction of 24-oxocholesteryl acetate with isopropylidenetriphenylphosphorane failed, probably because of severe steric hindrance and the tetrasubstituted nature of the resulting olefin.[8] Therefore, an alternative route was explored. 24-Acetylcholesteryl acetate (12)[5] by a Grignard reaction with methylmagnesium iodide afforded 28-hydroxy-24-isopropylcholesteryl acetate (10) in 47% yield. Dehydration of 10 with phosphorus oxychloride gave a mixture of olefins (4 and 5, in a 1:3 ratio by glc analysis), which was directly (without separation) treated with a 0.5 equiv of *m*-chloroperbenzoic acid. The expected epoxide (9) and the olefin (5) were separated in yields of 28 and 48% by column chromatography of the crude product.

Reaction of Epoxides with Acids.—Treatment of 6 with an excess of boron trifluoride etherate in benzene for 10 sec at room temperature yielded desmosteryl acetate (11, 35%), 24-acetylcholesteryl acetate (12, 45%), and 24-formyl-24-methylcholesteryl acetate [13, 12%, 9.53 ppm (s, 1 H)]. A reasonable pathway of this reaction is the following (Scheme I). Regiospecific

(1) This is part VI in the series of "Studies on Steroids." For part V see *Chem. Pharm. Bull.*, **21**, 457 (1973).

(2) D. N. Kirk and M. P. Hartshorn, "Steroid Reaction Mechanism," Elsevier, Amsterdam, 1968, Chapter 8, p 353.

(3) L. H. Briggs, J. P. Bartley, and P. S. Rutledge, *Tetrahedron Lett.*, 1237 (1970).

(4) N. Ikekawa, Y. Honma, N. Morisaki, and K. Sakai, *J. Org. Chem.*, **35**, 4145 (1970).

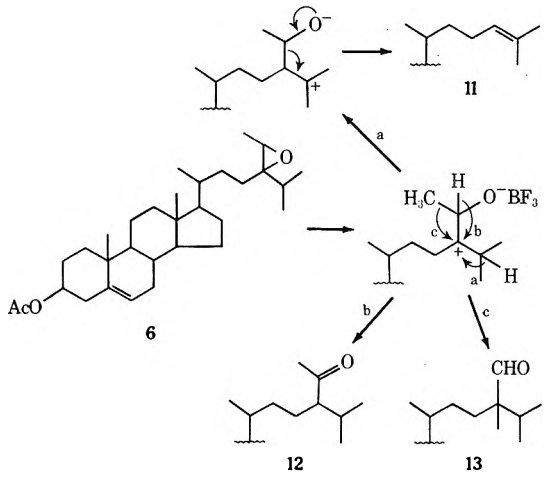
(5) N. Ikekawa, M. Morisaki, H. Ohtaka, and Y. Chiyoda, *Chem. Commun*, 1498 (1971).

(6) M. Morisaki, H. Ohtaka, M. Okubayashi, N. Ikekawa, Y. Horie, and S. Nakasone, *J. Chem. Soc., Chem. Commun.*, 1275 (1972).

(7) D. R. Idler and U. H. M. Fagerlund, *J. Amer. Chem. Soc.*, **79**, 1988 (1957).

(8) For a review of the Wittig reaction see A. Maercker, "Organic Reactions," Vol. 14, Wiley, New York, N. Y., 1965, p 270.

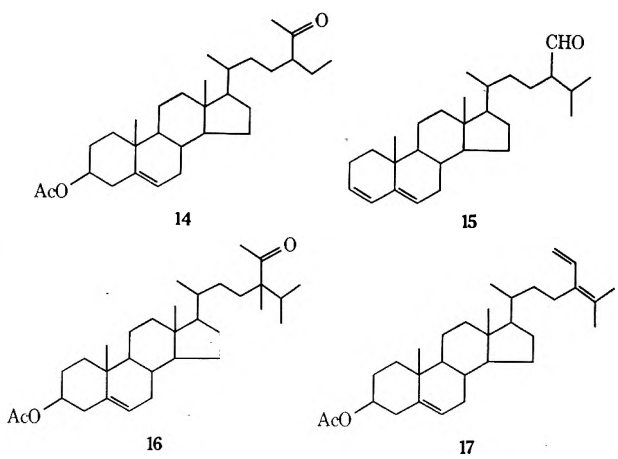
SCHEME I



epoxide ring opening of **6** would generate the tertiary carbonium ion at C-24, which, in turn, may be quenched in three ways: (a) migration of C-25 H with subsequent cleavage of C-24,28 bond to give **11**, (b) C-28 H shift to afford **12**, and (c) C-28 CH_3 shift to yield **13**. Rearrangement by route a would necessarily involve loss of acetaldehyde. Indeed, acetaldehyde was identified in the reaction mixture as its 2,4-dinitrophenylhydrazone by a glc analysis.

It was also suspected that the tertiary nature of the intermediate carbonium ion at C-25 may be one important factor in this fragmentation reaction.[9] This consideration appeared to be, at least partly, verified when similar treatment of epoxide (**8**) with boron trifluoride etherate was found to give 24-acetyl-26-norcholesteryl acetate (**14**) (Chart II) in theoretical yield,

CHART II



whereas, no 26-nordesmosteryl acetate was detected gas chromatographically.

(9) J. M. Coxon, M. P. Hartshorn, and D. N. Kirk, *Tetrahedron*, **25**, 1603 (1969). B. N. Blackett, J. M. Coxon, M. P. Harshorn, and K. E. Richards, *Tetrahedron Lett.*, 1737 (1969); *Tetrahedron*, **25**, 4999 (1969). I. G. Guest and B. M. Marples, *J. Chem. Soc. C*, 1626 (1970).

Recently, Morelli, *et al.*, reported an interesting fragmentation reaction of 3-isopropyl-3,5-epoxy-*A*-norcholestane with boron trifluoride etherate: I. Morelli, S. Catalano, G. Moretts, and A. Marsili, *Tetrahedron Lett.*, 717 (1972). They proposed a mechanism proceeding through an oxetane intermediate. If a similar oxetane could be formed from **6**, 26-nordesmosteryl acetate should be one of the reaction products. However, we could not find, by glc analysis, any material having a shorter retention time than **11**. Further, if the oxetane were an intermediate of the reaction of **9**, demosteryl should be the sole product.

In an attempt to assess the effect of a substituent at C-28 on this reaction, epoxides **7** and **9** were treated with boron trifluoride etherate. At room temperature, compound **7** reacted only sluggishly with boron trifluoride etherate. Starting material was recovered even on prolonged treatment (25 hr), while refluxing in benzene for 45 hr gave 24-formylcholesta-3,5-diene (**15**, 12%), uv 236.5 nm (ϵ 19,600), nmr δ 5.2–6.00 (m, 3 H) and 9.55 ppm (s, 1 H), as the sole isolable product, in addition to recovered starting compound. When compound **9** was treated with boron trifluoride etherate at room temperature for 10 sec, glc analysis of the product showed 24-acetyl-24-methylcholesteryl acetate (**16**), δ 1.97 (s, 3 H) and 2.00 ppm (s, 3 H), as the major component and a trace of **11**. The former was isolated in 22% yield by column chromatography on silicic acid.

Comparing the reactivity of four epoxides, it was found that the disubstituted one (**7**) reacted extremely slowly with boron trifluoride etherate compared with the tri- or tetrasubstituted epoxides (**6**, **8**, or **9**). Thus, even by refluxing the epoxide **7** in benzene for 30 hr, about half of unreacted starting material was recovered, whereas the other three epoxides were consumed completely within 10 sec at room temperature. All the isolated products (**11**–**16**) can be considered to be generated from the C-24 carbonium ion. This regiospecificity in the opening of the epoxide ring appears to be accomplished even in the case of **9**, which could give another tertiary carbonium ion at C-28. Another noteworthy feature of these reactions is the strong dependency of the fragmentation reaction on the substituents around the epoxide ring. Thus, only the epoxide **6**, but none of the analogous **7**, **8**, or **9**, seems to induce the fragmentation reaction.

Several Lewis acids and protonic acids were used to open the epoxide **6** in the hope of increasing the yield of desmosteryl acetate (**11**). However, the results summarized in Table I show that the optimum yield of **11** which never exceeded 35% was obtained with boron trifluoride etherate or $SnCl_4$.

When the epoxide **6** was refluxed with *p*-TsOH in benzene, a diene was obtained in 48% yield. The structure of this diene was deduced from its uv spectrum 235.5 nm (ϵ 18,600) and nmr 1.83 (s, 6H). The same diene **17** was generated from saringosteryl acetate[10] by dehydration with *p*-TsOH. A catalytic hydrogenation over PtO_2 gave tetrahydrofucosteryl acetate, proving no skeletal rearrangement during the reactions. The diene **17** seems to be a common reaction product of the epoxide **6** treated with protonic acids as shown in Table I.

Experimental Section[11]

24,28-Epoxystigmast-5-en-3β-yl Acetate (**6**).—A solution of 9.1 g of fucosteryl acetate[12] and 5.2 g of *m*-chloroperbenzoic acid in

(10) N. Ikekawa, K. Tsuda, and N. Morisaki, *Chem. Ind. (London)*, 1179 (1966).

(11) All melting points are uncorrected. Nmr spectra were recorded on a Varian T-60 spectrometer and mass spectra on a Hitachi RMU-6E and 7L spectrometer. Ir spectra were taken as KBr or liquid films on NaCl plates using a Hitachi EPI-G2 spectrometer, and uv spectra were obtained with an Hitachi ESP-3T spectrometer in ethanol solution. Glc analyses were performed on a Shimadzu GC-5APF gas chromatograph with a flame ionization detector.

(12) N. Ikekawa, N. Morisaki, K. Tsuda, and T. Yoshida, *Steroids*, **12**, 41 (1968).

TABLE I

PRODUCT DISTRIBUTION IN THE REACTION OF 24,28-EPOXYFUCOSTERYL ACETATE WITH VARIOUS ACIDS

Acids	Molar ratio of reagent	Solvent	Temp, °C	Time	Yields,[a] % Desmo 11	28-Keto 12	24-Formyl 13	24,28-Diene 17
Lewis acids								
BF_3–Et_2O	4	Benzene[b]	25	10 sec	33.6	34.8	27.6	
BF_3–Et_2O	0.15	Benzene	25	10 sec	7.6	20.3	25.1	
BF_3Et_2O	0.15	Benzene	25	1 hr	29.7	28.4	28.4	
$SnCl_4$	4	Benzene	25	1 hr	30.4	42.0	17.6	
$ZnBr_2$	4	Benzene	80	1 hr	14.4	30.7	38.9	
$AlCl_3$	4	AcOH	25	10 sec	7.6	59.4	trace	
BF_3 gas	L.E.[c]	CCl_4	25	10 sec	10.9	29.7	22.5	
BF_3 gas	L.E.	CCl_4	0	10 sec	2.5	54.7	21.6	
Protonic acids								
p-TsOH	4	Benzene	25	1 hr	4.1	30.7	19.6	26.5
AcOH[d]			25	10 min	2.9	34.3	41.4	13.3
CF_3COOH	4	Hexane	25	1 hr	12.0	26.1	23.2	24.7
PPA	L.E.	Hexane	25	1 hr	12.8	39.4	14.5	29.2

[a] Estimated from the peak area of gas chromatogram (1.5% OV-1 on Gas-Chrom P, 80–100 mesh, 180 cm × 4 mm i.d.; column temperature, 270°; carrier gas, N_2; flow rate, 80 ml/min). [b] The reaction is strongly dependent on solvent. Ether in place of benzene gave a complex mixture of products, whereas *n*-hexane seemed to afford a similar product distribution as in the case of benzene. [c] Large excess. [d] The reagent was used as a solvent.

300 ml of chloroform was stirred for 5 min at 0°. The reaction mixture was washed with 1 *N* NaOH and then with water and dried over Na_2SO_4. After removal of the solvent, the product was chromatographed on silica gel. The fraction eluted with hexane–benzene (1:3) afforded the epoxide 6 (6.9 g), which was crystallized from acetone: mp 101–103°; nmr ($CDCl_3$) δ 0.67 (s, 3, C-18 H), 0.85–0.95 (m, 9), 1.01 (s, 3, C-19 H), 1.25 (d, 3, J = 6 Hz, C-29 H), 2.02 (s, 3, OAc), 2.88 (q, 1, J = 6 Hz, C-28 H), 4.60 (m, 1, C-3 H), 5.35 (m, 1, C-6 H); mass spectrum m/e 410 (M^+ − AcOH). *Anal.* Calcd for $C_{31}H_{50}O_3$: C, 79.10; H, 10.71. Found: C, 79.16; H, 10.63.

Reaction of 24,28-Epoxystigmast-5-en-3β-yl Acetate with Boron Trifluoride Etherate.—24,28-Epoxystigmast-5-en-3β-yl acetate (6, 270 mg) in 5 ml of dry benzene was treated with 0.5 ml of boron trifluoride etherate for 10 sec at room temperature. The solution was washed with saturated $NaHCO_3$, then with water, and dried over Na_2SO_4. The solvent was distilled off and the crude product was chromatographed on silica gel.

The fraction eluted with benzene–hexane (1:4) gave 95 mg of desmosteryl acetate, mp 114–116° (from acetone), identified by comparison with the authentic sample.

The fraction eluted with benzene–hexane (1:1) gave 32 mg of 24-formyl-24-methylcholesteryl acetate (13): mp 128–131° (from acetone); nmr ($CDCl_3$) δ 0.67 (s, 3, C-18 CH_3), 0.90 (s, 6), 0.96 (s, 3), 1.02 (s, 6), 2.03 (s, 3, OAc), 4.60 (m, 1, C-3 H), 5.40 (m, 1, C-6 H), 9.53 ppm (s, 1, CHO); ir 1710 cm^{-1}; mass spectrum m/e 410.3493 (M^+ − AcOH) (calcd 410.3548). Compound 13 (9 mg) in methanol (1 ml) was treated with excess $NaBH_4$ at room temperature for 30 min. After usual work-up, the 24-hydroxymethyl derivative was obtained: mp 129–132° (from methanol); nmr ($CDCl_3$) 0.67 (s, 3), 0.73 (s, 3), 0.77–0.97 (m, 6), 1.00 (s, 6), 2.03 (s, 3), 3.43 (s, 2, CH_2OH), 4.60 (m, 1), 5.37 ppm (m, 1).

The fraction eluted with benzene–hexane (3:1) gave 125 mg of 24-acetylcholesteryl acetate: mp 130–132° (from acetone); nmr ($CDCl_3$) δ 0.66 (s, 3), 0.85–1.05 (m, 12), 2.01 (s, 3), 2.08 (s, 3, C-24 Ac), 4.55 (m, 1), 5.33 ppm (m, 1); ir 1710, 1725 cm^{-1}. *Anal.* Calcd for $C_{31}H_{50}O_3$: C, 79.10; H, 10.71. Found: C, 79.05; H, 10.73.

Identification of Acetaldehyde.—To the reaction mixture of 24,28-epoxystigmast-5-en-3β-yl acetate (5 mg) with boron trifluoride etherate (5 μl) in benzene (1 ml), a solution of 2,4-dinitrophenylhydrazine (0.01 g) in diglyme (0.3 ml) and concentrated HCl (1 drop) was added. The mixture was extracted with benzene. The extract was analyzed by a glc using 1.5% OV-1 and 1.5% OV-17 on Chromosorb W, 80–100 mesh, as the column packings (column size, 180 cm × 4 mm i.d.; column temperature, 200°). One of the prominent peaks corresponded with the 2,4-dinitrophenylhydrazone of acetaldehyde.

26-Norfucosteryl Acetate (3).—A mixture of triphenylphosphinethyl bromide (0.5 g), *n*-butyllithium (1.5% w/v, 0.6 ml), and dry ether (6 ml) was shaken under nitrogen atmosphere in a pressure bottle for 30 min at room temperature. To the ylide solution, 24-oxo-26-norcholesteryl acetate[4] (185 mg) was added and the mixture was allowed to stand for 23 hr at 80°. After the usual work-up the product was acetylated with excess of acetic anhydride and pyridine and then chromatographed on silica gel. Elution with benzene–hexane (1:5) afforded 36 mg of 3: mp 126–129° (from methanol–acetone); nmr ($CDCl_3$) δ 0.67 (s, 3), 0.99–1.10 (m, 9), 1.60 (d, 3, J = 7 Hz, C-29 CH_3), 2.00 (s, 3), 4.60 (m, 1), 5.17 (q, 1, J = 7 Hz, C-28 H), 5.40 ppm (m, 1); mass spectrum m/e 380.3416 (M^+ − AcOH) (calcd 380.3443). Elution with benzene–hexane (3:1) afforded 89 mg of starting material.

24,28-Epoxy-26-norstigmast-5-en-3β-yl Acetate (8).—26-Norfucosteryl acetate (30 mg) in 1 ml of chloroform was treated with 17 mg of *m*-chloroperbenzoic acid at 0° for 3 min. The product was chromatographed on silica gel. Elution with benzene–hexane (1:5) afforded 5 mg of recovered starting material. Elution with benzene–hexane (1:1) afforded 22 mg of 8: mp 135–137° (from methanol–acetone); nmr ($CDCl_3$) δ 0.67 (s, 3), 0.87–1.10 (m, 9), 1.27 (d, 3, J = 6 Hz, C-29 CH_3), 2.02 (s, 3), 2.83 (q, 1, J = 6 Hz, C-28 H), 4.60 (m, 1), 5.40 ppm (m, 1); mass spectrum m/e 396.3371 (M^+ − AcOH) (calcd 396.3392).

Reaction of 8 with Boron Trifluoride Etherate.—8 (10 mg) in dry benzene (2 ml) was treated with 10 μl of boron trifluoride etherate for 10 sec at room temperature. The solution was washed with saturated $NaHCO_3$, then with water, and dried over Na_2SO_4. Removal of the solvent afforded 10 mg of 24-acetyl-26-norcholesteryl acetate as a sole product: mp 133.5–134.5°; nmr ($CDCl_3$) δ 0.67 (s, 3), 0.83–1.10 (m, 9), 2.03 (s, 3), 2.10 (s, 3, C-24 Ac), 4.60 (m, 1), 5.40 ppm (m, 1); mass spectrum m/e 396.3371 (M^+ − AcOH) (calcd 396.3392).

24,28-Epoxy-24-methylenecholesteryl Acetate (7).—24-Methylenecholesteryl acetate (2) was prepared from 24-oxocholesteryl acetate with triphenylphosphinemethyl bromide by a Wittig reaction. The yield was increased to 85% by heating the reaction mixture at 120° for 24 hr, instead of room temperature as reported.[7]

2 (1 g) in 50 ml of chloroform was treated with *m*-chloroperbenzoic acid (450 mg) at 0° for 3.5 hr. After the usual work-up the product was chromatographed on silical gel. Elution with benzene–hexane (1:2) afforded 200 mg of the starting material. Elution with benzene–hexane (1:1) afforded 190 mg of 7: mp 134–136° (from methanol); nmr (CCl_4) δ 0.67 (s, 3), 0.80–1.02 (m, 12), 1.93 (s, 3), 2.39 (s, 2, C-28 H), 4.48 (m, 1), 5.42 ppm (m, 1). *Anal.* Calcd for $C_{30}H_{48}O_3$: C, 78.89; H, 10.59. Found: C, 78.99; H, 10.63.

Reaction of 7 with Boron Trifluoride Etherate.—A solution of 100 mg of 7 and 110 μl of boron trifluoride etherate in 20 ml of benzene was refluxed for 45 hr. After the usual work-up, the crude product was chromatographed on silica gel column. Elution with benzene–hexane (1:6) afforded 9.4 mg of 24-formylcholesta-3,5-diene (15): mp 94–99° (amorphous); nmr ($CDCl_3$) δ 0.67 (s, 3), 0.87–1.03 (m, 12), 5.62–6.0 (m, 3, C-3,4,6 H), and 9.55 ppm (s, 1, 24-CHO); uv max 236.5 nm (ε 19,600); ir 1715

cm^{-1}; mass spectrum *m/e* 396 (M^+). Elution with benzene–hexane (2:1) afforded 12 mg of the starting material.

28-Hydroxy-24-isopropylcholesteryl Acetate (10).—A solution of 250 μl of methyl iodide in 1 ml of dry ether was added dropwise to 96 mg of magnesium turnings under nitrogen atmosphere. After the spontaneous reaction began, another 5 ml of dry ether was added, and the mixture was stirred for 45 min. To the solution 800 mg of **12** in 5 ml of ether was added dropwise in 15 min and the solution was refluxed for 1.5 hr. After the usual work-up, the product was acetylated with excess acetic anhydride and pyridine and chromatographed on silica gel. Elution with benzene–hexane (2:1) afforded 237 mg of the starting material. Elution with benzene–hexane (10:1) afforded 28-hydroxy-24-isopropylcholesteryl acetate (**10**, 387 mg): mp 132–135° (from acetone); nmr (CCl_4) δ 0.62 (s, 3), 0.73–1.00 (m, 12), 1.07 (s, 6, C-29 CH_3, C-30 CH_3), 1.89 (s, 3), 4.50 (m, 1), 5.30 (m, 1); mass spectrum *m/e* 426.3849 (M^+ − AcOH) (calcd 426.3861).

24,28-Epoxy-28-methylstigmast-5-en-3β-yl Acetate (9).—To the solution of 150 mg of **10** in 3 ml of pyridine, 0.3 ml of phosphorus oxychloride was added, and the mixture was allowed to stand overnight at room temperature. After the usual work-up, the product was dissolved in 10 ml of chloroform and treated with 35 mg of *m*-chloroperbenzoic acid at 0° for 10 min. The product was chromatographed on silica gel. Elution with benzene–hexane (1:10) afforded 82 mg of 24-isopropylcholesta-5,28-dien-3-ol acetate (**5**): mp 128–131° (from acetone); nmr (CCl_4) δ 0.63 (s, 3), 0.80–1.03 (m, 12), 1.53 (s, 3), 1.90 (s, 3), 4.55 (m, 1), 4.59 (s, 1, C-29 H), 4.70 (s, 1, C-29 H), 5.33 ppm (m, 1); mass spectrum *m/e* 408.3724 (M^+ − AcOH) (calcd 408.375). Elution with benzene–hexane (3:1) afforded 48 mg of **9**: mp 103–105° (amorphous); nmr (CCl_4) δ 0.67 (s, 3), 0.83–1.13 (m, 12), 1.22 (s, 3), 1.26 (s, 3), 1.95 (s, 3), 4.55 (m, 1), 5.30 ppm (m, 1); mass spectrum *m/e* 424.3671 (M^+ − AcOH) (calcd 424.3704).

Reaction of 9 with Boron Trifluoride Etherate.—**9** (30 mg) in 6 ml of benzene was treated with boron trifluoride etherate (30 μl) for 10 sec at room temperature. After the usual work-up, the product was chromatographed on silica gel. Elution with benzene–hexane (1:3) afforded 6.6 mg of 24-acetyl-24-methylcholesteryl acetate (**16**): mp 115–120° (from methanol); nmr ($CDCl_3$) δ 0.67 (s, 3), 0.80 (s, 3), 0.90 (s, 6), 1.00 (s, 6), 1.97 (s, 3), 2.00 (s, 3, C-24 Ac), 4.60 (m, 1), 5.40 ppm (m, 1); ir 1690, 1715 cm^{-1}; mass spectrum *m/e* 424.3671 (M^+ − AcOH) (calcd 424.3704).

24-Ethylcholesta-5,24,28-trien-3β-ol Acetate (17).—A solution of 1 g of **6** and 65 mg of *p*-toluenesulfonic acid in 30 ml of benzene was refluxed for 30 min. After usual work-up of the mixture, the crude product was chromatographed on silica gel. The fraction eluted with benzene–hexane (1:1) gave 487 mg of **17**: mp 109–111°; nmr ($CDCl_3$) δ 0.69 (s, 3), 1.02 (s, 6), 1.83 (m, 6, C-26 and C-27 CH_3), 2.02 (s, 3), 4.60 (m, 1), 4.80–5.06 (m, 2, C-29 H_2), 5.38 (m, 1, C-28 H), 5.64 ppm (m, 1); uv max 235.5 nm (ε 18,600); mass spectrum *m/e* 452.3677 (M^+) (calcd 452.3654).

Compound **17** (50 mg) was dissolved in 1 ml of acetic acid and hydrogenated over 5 mg of platinum dioxide. Three mole equivalents of hydrogen was absorbed over a period of 1 hr. After removal of the catalyst, the filtrate was made alkaline with NaOH solution and the precipitate crystallized from acetone, mp 123–126°. The melting point and ir and nmr spectra were identical with those of tetrahydrofucosteryl acetate prepared from fucosteryl acetate by the same procedure.

Compound **17** was unstable to light. After a 1-day exposure to light in the laboratory, the major part had decomposed, but it was stable when refrigerated in a dark bottle.

Dehydration of Saringosteryl Acetate.—A solution of 517 mg of saringosteryl acetate and 27 mg of *p*-toluenesulfonic acid in 15 ml of benzene was refluxed for 30 min. After the usual work-up, the crude product was chromatographed on silica gel. The fraction eluted with benzene–hexane (1:3) afforded prisms from acetone of mp 109–111°. The compound's melting point, mixture melting point, and nmr spectrum agreed with those of compound **17**.

Registry No.—**3**, 38863-83-1; **5**, 38863-84-2; **6**, 35458-70-9; **7**, 35458-74-3; **8**, 38863-87-5; **9**, 38863-88-6; **10**, 38863-89-7; **11**, 2665-04-5; **12**, 38863-91-1; **13**, 38863-92-2; **13** (24-hydroxymethyl derivative), 38863-93-3; **14**, 38863-94-4; **15**, 38863-95-5; **16**, 38863-96-6; **17**, 38863-97-7; fucosteryl acetate, 6035-62-7; boron trifluoride etherate, 109-63-7; 24-oxo-26-norcholesteryl acetate, 26308-99-6; 24-oxocholesteryl acetate, 20981-59-3.

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Stereospecific Synthesis of Cis and Trans Epoxides from the Same Diol

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From the benzaldehyde acetal of *meso*-2,3-butanediol, isomerically pure *cis*-2,3-epoxybutane was synthesized by treatment with *N*-bromosuccinimide in carbon tetrachloride, followed by treatment with potassium hydroxide; isomerically pure *trans*-2,3-epoxybutane was synthesized by treatment with *N*-bromosuccinimide in water, followed by treatment with *p*-toluenesulfonyl chloride, followed by treatment with potassium hydroxide. From these reactions and the treatment of other cyclic acetals with *N*-bromosuccinimide, the reaction was shown to be ionic, kinetically regiospecific, and specific for the acetal carbon.

The recently reported stereospecific syntheses of halohydrin esters and epoxides by Newman and Chen[2] prompt us to report our preliminary results on a related stereospecific epoxide synthesis. Treatment of the readily accessible acetal of benzaldehyde and *meso*-2,3-butanediol[3] with *N*-bromosuccinimide[4] (NBS) in carbon tetrachloride containing a trace of HBr followed by treatment of the resulting bromohydrin ester[5] with potassium hydroxide in ethylene glycol gives *cis*-2,3-epoxybutane isomerically pure by nmr (Scheme I). Treatment of the same acetal with NBS in water, followed by treatment of the tosylate derived from the resulting glycol monoester with potassium hydroxide in ethylene glycol and 1,2-dimethoxyethane, gives *trans*-2,3-epoxybutane isomerically pure by nmr (Scheme II).

(1) Participant in ACS Seed Catalyst Program, summer, 1971.

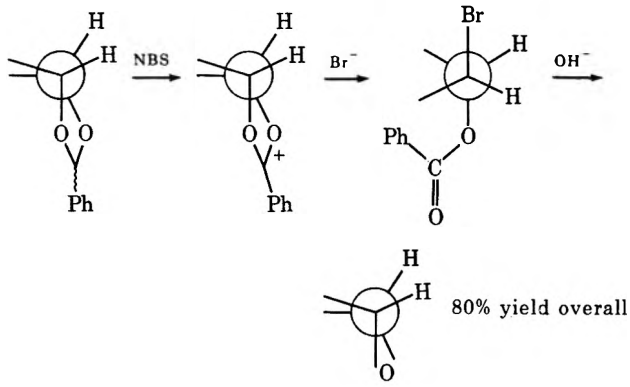
(2) M. S. Newman and C. H. Chen, *J. Amer. Chem. Soc.*, **94**, 2149 (1972).

(3) D. Gagnaire and J.-B. Robert, *Bull. Soc. Chim. Fr.*, 3646 (1965).

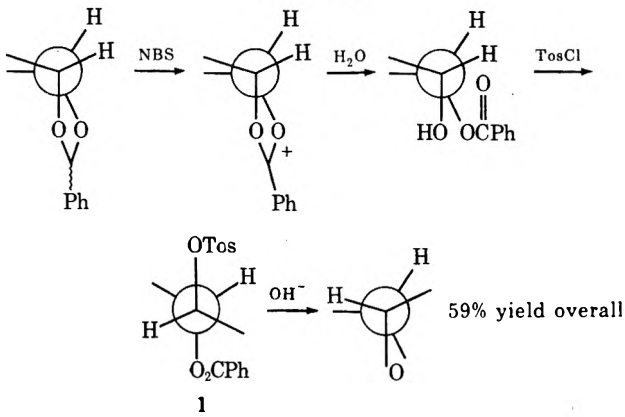
(4) For other examples of bromination of 1,3-dioxolanes, see ref 6 and papers cited therein; T. L. Hullar and S. B. Siskin, *J. Org. Chem.*, **35**, 225 (1970), and M. M. Ponpipom and S. Hanessian, *Can. J. Chem.*, **50**, 253 (1972), for uses in sugar and nucleoside chemistry; and D. H. R. Barton, L. Bould, D. L. C. Clive, P. D. Magnus, and T. Hase, *J. Chem. Soc. C*, 2204 (1971).

(5) Satisfactory ir, nmr, and low-resolution mass spectral data were obtained for each new compound. A satisfactory elemental analysis was obtained for compound **1**; all other compounds gave satisfactory high-resolution mass spectra.

SCHEME I



SCHEME II

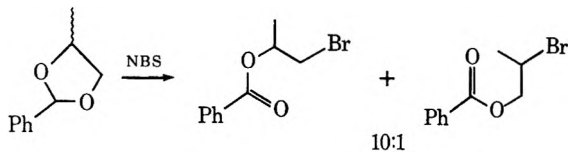


Hence either the cis or trans epoxide may be made at will from the same glycol.

That the oxidation of the dioxolane involves a dioxolenyl cation rather than radical is shown by the absence of bromo ester or 2-butyl benzoate in Scheme II and the absence of chloro ester in Scheme I.[6] When the acetal made from a mixture of 60% *dl*- and 40% *meso*-2,3-butanediol is treated with NBS in carbon tetrachloride, the erythro bromohydrin ester predominates.[7] When the acetal is treated with NBS in water, the threo glycol monoester predominates.[8] Hence there is no cis–trans isomerization of the dioxolane or dioxolenium rings before cleavage.

An explanation of the difference in the stereochemistry of the ring opening by water *vs.* bromide was advanced by Perst, as depicted in Scheme III.[9]

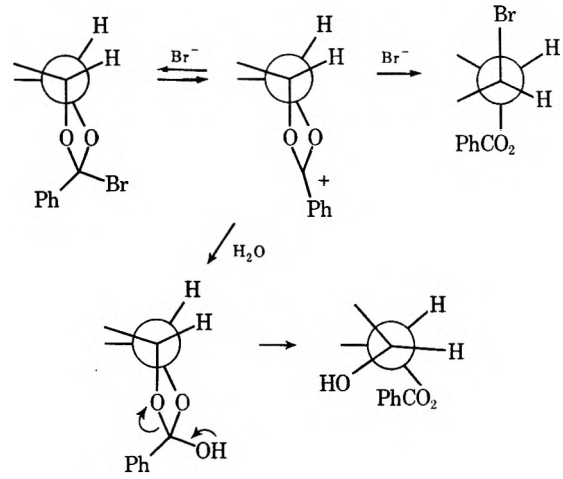
Regiospecificity similar to that of Newman and Chen[2] was observed on bromination of 4-methyl-2-phenyl-1,3-dioxolane in carbon tetrachloride with NBS and a trace of HBr at room temperature.[6] This ratio is apparently



kinetically controlled, since upon heating this reaction mixture or the 3:1 mixture of bromo benzoates resulting

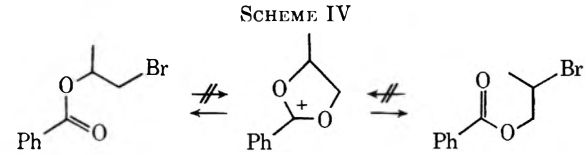
(6) *Cf.* J. D. Prugh and W. C. McCarthy, *Tetrahedron Lett.*, 1351 (1966).
(7) Assayed by nmr of the resultant epoxide: 40% cis and 60% trans.
(8) Assayed by glc (10% SE-30, 100°) of the acetonides of the glycols resulting from saponification of this ester: ~70% threo and 30% erythro.
(9) H. Perst, "Oxonium Ions," Academic Press, New York, N. Y., 1971, p 80 ff.

SCHEME III



from reaction of benzoyl bromide with practical 1-bromo-2-propanol (consisting of 75% 1-bromo-2-propanol and 25% 2-bromo-1-propanol) in carbon tetrachloride at 70° for 12 hr, no significant change in the ratio of isomers is observed by nmr; *i.e.*, the reverse reactions (Scheme IV) do not occur under the reaction conditions.

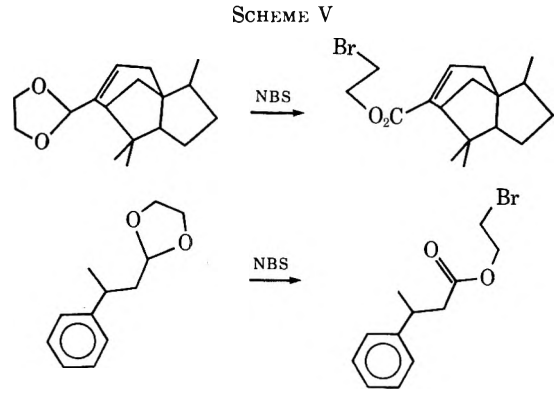
SCHEME IV



Note that, since there is no crossover of *dl*-2,3-butanediol-derived products to *meso*-2,3-butanediol-derived products, or vice versa, the conversion of either *d*- or *l*-2,3-butanediol to epoxide *via* Scheme I would result in no racemization and would give the enantiomerically pure epoxide.

The chemical specificity of this bromination is demonstrated in the reaction of cedrenaldehyde and 3-phenylbutyraldehyde ethylene acetals with NBS in carbon tetrachloride (Scheme V). In no case were any

SCHEME V



products resulting from the bromination of the allylic or benzylic positions detected by nmr.

One of the useful features of being able to generate either the cis or trans epoxide from a given diol is that the epoxides are intermediates for stereospecific deoxygenation to the olefins. We are now pursuing ways to generate cis or trans olefins at will directly from a given bromohydrin ester.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 257 spectrometer. All nmr spectra were recorded on a Varian A-60A spectrometer. Mass spectra were recorded on a AEI MS-901/Digital PDP-8/I system. The elemental analysis was performed by Meade Microanalytical Laboratory, Amherst, Mass. Gas chromatographic analyses and preparations were made on a modified Wilkens Aerograph A-90-P/Varian Aerograph 700 gas chromatograph.

Cedren-15-aldehyde Ethylene Acetal.—A mixture of 5.57 g (25.6 mmol) of cedren-15-aldehyde,[10] 1.60 g (25.8 mmol) of ethylene glycol, 3.79 g (25.6 mmol) of triethyl orthoformate, and *ca.* 10 mg of *p*-toluenesulfonic acid was heated slowly to 140° while the volatile products were distilled through a short-path still at atmospheric pressure. When the head temperature reached 85° the remaining mixture was distilled *in vacuo* to give 3.0 g of mixture (70% acetal by gc[11]), bp 102–128° (0.10 mm), and 2.5 g of pure acetal, bp 128° (0.10 mm), in 68% yield (total): nmr (CCl_4) δ 0.90 (d, 3, J = 7 Hz), 0.98 (s, 3), 1.02 (s, 3), 1.2–2.3 (m, 11), 3.8 (m, 4), 5.05 (s, 1), 5.68 (t, 1, J = 3 Hz); m/e 262.1912 (calcd for $C_{17}H_{26}O_2$, 262.1932).

3-Phenylbutyraldehyde Acetal.—A mixture of 2.00 g (13.5 mmol) of 3-phenylbutyraldehyde [prepared by reduction of ethyl 3-phenylbutyrate[12] with diisobutylaluminum hydride by the method of Zakharkin and of Khorlina[13], bp 83–84° (2.8 mm) [lit.[14] bp 115° (18 mm)] in 86% yield], 1.3 g (21 mmol) of ethylene glycol, and 10 mg of *p*-toluenesulfonic acid in 50 ml of benzene was heated at reflux in a Dean–Stark apparatus for 15 hr. The mixture in the pot was diluted with 50 ml of ether, washed with 30 ml of saturated aqueous $NaHCO_3$ solution, dried over K_2CO_3, concentrated on a rotating evaporator, and distilled *in vacuo* to give 2.18 g (84%) of acetal: bp 88–94° (0.8 mm); nmr (CCl_4) δ 1.25 (d, 3, J = 7 Hz), 1.8 (m, 2), 2.93 (sextet, 1, J = 7 Hz), 3.76 (m, 4, A_2B_2), 4.56 (d × d, 1, J = 4, 6 Hz), 7.13 (s, 5); m/e 192.1169 (calcd for $C_{12}H_{16}O_2$, 192.1150).

Bromination of 4,5-Dimethyl-2-phenyl-1,3-dioxolane in CCl_4.—To a slurry of 21.0 g (0.118 mol) of *N*-bromosuccinimide (NBS) in 250 ml of CCl_4 cooled in an ice bath, 21.0 g (0.118 mol) of 4,5-dimethyl-2-phenyl-1,3-dioxolane[2] [prepared by the triethyl orthoformate method (above) in 98% yield from 2,3-butanediol (56% threo and 44% erythro by gc[15] of acetonide), bp 153–157° (56 mm)] was added slowly. The mixture was stirred in darkness for 16 hr at room temperature, after which all of the NBS was observed to have reacted (this reaction time varies, without apparent pattern, from 2 hr to 1 week). The reaction mixture was filtered, washed twice with 60 ml of saturated aqueous $NaHCO_3$ solution, dried with Na_2SO_4, and concentrated on a rotating evaporator to 33.7 g of yellow oil (111% of theory). A sample was purified by distillation *in vacuo* for analysis: bp 112–113° (1.6 mm); ir (neat) 1725 and 1270 cm^{-1}; nmr (CCl_4) δ 1.60 (d, 3, J = 6.5 Hz), 1.72 (d, 3, J = 7 Hz), 4.21 (m, 1), 5.17 (m, 1), 7.4 (m, 3), 8.0 (m, 2); m/e 258.0051 (calcd for $C_{11}H_{13}Br^{81}O_2$, 258.0078). The nmr spectrum of an analytical sample prepared from the bromination of 4,5-dimethyl-2-phenyl-1,3-dioxolane prepared from *erythro*-2,3-butanediol differs only in the multiplets at δ 4.12 and 5.17, which are simplified to 4.21 (d × q, 1, J = 4, 7 Hz) and 5.17 (d × q, 1, J = 4, 6 Hz).

Saponification of Crude 2-(3-Bromobutyl) Benzoate.—A mixture of 1.9 g (47 mmol) of NaOH and 5.32 (20.7 mmol) of 2-(3-bromobutyl) benzoate in 15 ml of ethylene glycol was gradually heated to 140° while the product was distilled through a short-path still, giving 1.19 g of clear liquid, bp 59° (740 mm), which was analyzed by nmr to be 35% *cis*- and 55% *trans*-2,3-epoxybutane and 10% ethylene glycol. The yield from 4,5-dimethyl-2-phenyl-1,3-dioxolane was 111% × 72% or 80%.

Bromination of 4,5-Dimethyl-2-phenyl-1,3-dioxolane in H_2O.—To a mixture of 13.51 g (76.1 mmol) of NBS, 1 drop of concentrated hydrobromine acid, and 130 ml of H_2O cooled in an ice bath, 13.51 g (76.1 mmol) of 4,5-dimethyl-2-phenyl-1,3-dioxolane (prepared from a mixture of *erythro*- and *threo*-2,3-butanediols) was added slowly. After being stirred for 1 hr, the reaction mixture was still red, so *ca.* 2 g of $NaHCO_3$ was added, and the mixture was stirred for 17 hr at room temperature, then extracted with 3 × 100 ml portions of ether which were combined, dried with Na_2SO_4, and concentrated to *ca.* 20 ml of yellow oil. The oil was distilled *in vacuo* to give 12.58 g (85%) of 2-(3-hydroxybutyl) benzoate: bp 108–115° (0.5 mm); ir (neat) 3450 and 1720 cm^{-1}; nmr ($CDCl_3$) δ 1.25 (d, 3, J = 7 Hz), 1.34 (d, 3, J = 5 Hz), 2.9 (s, 1), 3.95 (m, 1), 5.07 (m, 1), 7.45 (m, 3), 8.1 (m, 2); m/e 194.0964 (calcd for $C_{11}H_{14}O_3$, 194.0942).

2-(3-Benzoyloxybutyl) *p*-Toluenesulfonate.—To 0.88 g (4.53 mmol) of 2-(3-hydroxybutyl) benzoate in 12 ml of pyridine, 1.74 g (9.11 mmol) of freshly recrystallized *p*-toluenesulfonyl chloride was added. The mixture was allowed to stand at room temperature for 24 hr, then was diluted with 50 ml of ether. The solution was washed successively with 3 × 10 ml of dilute (1:1) HCl solution, 2 × 10 ml of saturated aqueous $NaHCO_3$ solution, and 10 ml of H_2O, dried over $MgSO_4$, and concentrated on a rotating evaporator to a white solid which was recrystallized from ether and petroleum ether (bp 30–60°) to give 1.13 g (72%) of tosylate: mp 81–82° (uncorrected); nmr ($CDCl_3$) δ 1.30 (d, 3, J = 7 Hz), 1.38 (d, 3, J = 6.5 Hz), 2.31 (s, 3), 4.9 (m, 2), 7.0–8.0 (m, 9).

Anal. Calcd for $C_{18}H_{20}O_5S$: C, 62.05; H, 5.79. Found: C, 62.17; H, 6.04.

Saponification of 2-(3-Benzoyloxybutyl) *p*-Toluenesulfonate.—A mixture of 3.76 g (10.8 mol) of tosylate and 6.5 ml of *ca.* 1.4 *M* KOH in 1,2-dimethoxyethane (glyme) solution in 12 ml of glyme was stirred at room temperature for 1 hr and then distilled at room temperature *in vacuo* (50 mm) with a cold trap immersed in Dry Ice–acetone. After 14 hr at 50 mm the reaction pot was heated at 50° and the pressure was lowered to 25 mm for 1 hr. The contents of the trap (9.67 g) were analyzed by nmr to be 6.80 wt % 2,3-epoxybutane in glyme, a net yield of 97%.

Registry No.—Cedren-15-aldehyde ethylene acetal, 38739-76-3; cedren-15-aldehyde, 30960-40-8; ethylene glycol, 107-21-1; triethyl orthoformate, 122-51-0; 3-phenylbutyraldehyde ethylene acetal, 38739-78-5; 3-phenylbutyraldehyde, 16251-77-7; *N*-bromosuccinimide, 128-08-5; 4,5-dimethyl-2-phenyl-1,3-dioxolane, isomer A, 13165-94-1; 4,5-dimethyl-2-phenyl-1,3-dioxolane, isomer B, 4359-31-3; erythro-2-(3-bromobutyl) benzoate, 38822-42-3; threo-2-(3-bromobutyl) benzoate, 38739-82-1; *cis*-2,3-epoxybutane, 1758-33-4; *trans*-2,3-epoxybutane, 6189-41-9; *erythro*-2-(3-hydroxybutyl) benzoate, 38739-85-4; *threo*-2-(3-hydroxybutyl) benzoate, 38739-86-5; *erythro*-2-(3-benzoyloxybutyl) *p*-toluenesulfonate, 38739-87-6; *threo*-2-(3-benzoyloxybutyl) *p*-toluenesulfonate, 38739-88-7; *p*-toluenesulfonyl chloride, 98-59-9.

Acknowledgment.—We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

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(11) 10% SE-30 Chromosorb P AW-DMCS at 260°.
(12) V. K. Honwad and A. S. Rao, *Tetrahedron*, **21**, 2593 (1965).
(13) L. A. Zakharkin and I. M. Khorlina, *Tetrahedron Lett.*, 619 (1962).
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(15) 10% SE-30 Chromosorb P AW-DMCS at 110°.

Preparation and Stereochemistry of the Methyl 1,3-Dimethylcyclohexaneacetates and Related Compounds

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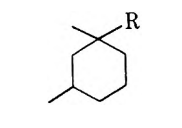
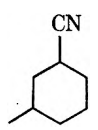
The two methyl 1,3-dimethylcyclohexaneacetates (**6e** and **7e**) have been prepared by Arndt–Eistert synthesis from the related cyclohexanecarboxylic acids **6b** and **7b**. Concomitant formation in this synthesis of the rearrangement products **11** and **12** from **6b** rigorously establishes the stereochemistry of these compounds. The assignment is in accord with data reported here from independent syntheses, nmr spectra, and vpc retention times. It leads to reversal of the assignment made earlier for **6b** and **7b** and methyl ketones **4**, and it suggests that the stereochemistry proposed for keto esters **19** and **20** may be in error.

In examining the steric course of certain photochemical reactions we required authentic samples of both diastereomers of 1,3-dimethylcyclohexaneacetic acid methyl ester (**1**). In this report we describe the preparation and rigorous assignment of stereochemistry for these esters, as well as for the related cyclohexanecarboxylic acids **2** and esters **3**. In the only pertinent earlier work[1] the stereochemistry of the methyl ketones **4** was deduced from their viscosities and from the failure of one isomer to yield a semicarbazone; each of these ketones was then degraded to the corresponding isomer of acid **2** by hypobromite oxidation. Our present assignments require reversal of these earlier conclusions.

The first line of evidence comes from alkylation of the lithium salt of 3-methylcyclohexanecarbonitrile (**5**)[2] with methyl iodide in dimethoxyethane. The 7:3 mixture of isomeric products formed in 89% yield was separated by preparative vapor phase chromatography (vpc), and each nitrile was fully characterized. Structures **6a** and **7a** can be assigned with reasonable confidence to the major and minor isomer, respectively, since alkylation of the *tert*-butyl-substituted nitrile **8** under these conditions yields a 71:29 mixture of **9** and **10**.[3] Nitriles **6a** and **7a** were then hydrolyzed



1, R = $CH_2CO_2CH_3$
2, R = CO_2H
3, R = CO_2CH_3
4, R = $COCH_3$



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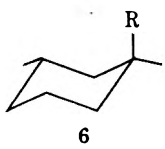

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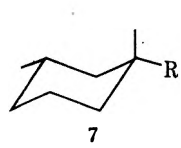
a, R = CN
b, R = CO_2H
c, R = CO_2CH_3



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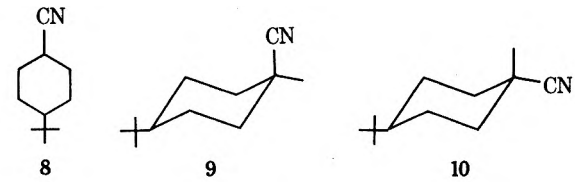
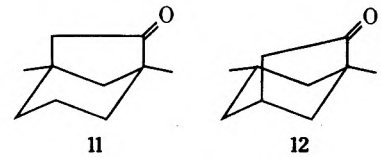
d, R = $COCHN_2$
e, R = $CH_2CO_2CH_3$

in strong base to the corresponding crystalline carboxylic acids **6b**, mp 88.5–89.5°, and **7b**, mp 45–46°.

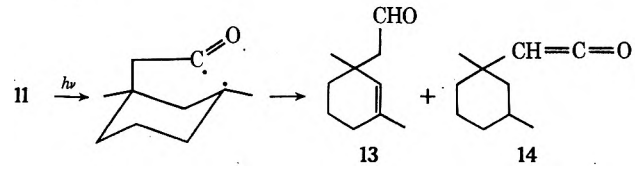
A most convincing confirmation of this stereochemical assignment comes from the Arndt–Eistert homologation of these acids **6b** and **7b**. Each was converted through the acyl chloride to the diazo ketone in the usual manner,[4] and these diazo ketones **6d** and **7d** were then treated[5] with silver benzoate and triethylamine in methanol. While **7d** gave the desired homologous ester **7e** without incident, the attempted Wolff rearrangement of **6d** gave some **6e** along with two ketones. On the basis of the spectroscopic properties detailed in the Experimental Section and the degradative correlation described below, we assign structures **11** and **12** to these substances. These are then carbon–hydrogen insertion products from so-called anomalous Wolff rearrangement, a process which has already received attention in closely related systems.[6] The structure of **11** was verified by a photochemical degradation.[7] Irradiation ($\lambda > 2800$ Å) of **11** in benzene led to α cleavage and subsequent hydrogen transfer, with formation of aldehyde **13** and ketene **14**. The



8 **9** **10**



11 **12**



13 **14**

latter reacted with methanol to give the corresponding ester, which was isolated and shown to be **6e** by comparison with a sample from the Arndt–Eistert synthesis. This correlation securely establishes the structure of ketone **11**. The formation of these insertion products **11** and **12** from **6d** rigorously defines, in turn, the stereochemistry in this series.

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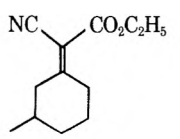
We have also independently prepared **6e** from 3-methylcyclohexanone by a sequence previously used with cyclohexanone[8] and 4,4-dimethylcyclohexanone.[7] Knoevenagel reaction between the ketone and cyanoacetic ester furnished **15** (geometry undetermined), which underwent stereoselective addition of methylmagnesium iodide in the presence of copper(I) catalyst to yield **16**. This was converted to **6e** through saponification and decarboxylation, followed by esterification with diazomethane. The exclusive equatorial 1,4 addition to **15** observed here is analogous to the stereoselective conversion of **17** under similar conditions (or using lithium dimethylcuprate) into **18**.[9]

These stereochemical deductions are all in complete accord with evidence from nmr spectra and vpc retention times. In the 220-MHz spectra of both acid **6b** and the derived methyl ester **6c** the resonance of two of the ring protons is shifted downfield and appears at δ 2.25 ppm (broad, 2 H). We ascribe this signal to the two protons in an axial 1,3 relation to, and somewhat deshielded by, the carbonyl group of these compounds. No such shifted signal appears for **7b** and **7c**, in which the carbonyl group is preferentially equatorial. Also the equatorial methyl substituent at C-1 in **6b**, **6c**, and **6e** is characterized by the expected[10] small upfield shift (Δ 0.02–0.06 ppm) of resonance relative to the axial methyl of **7b**, **7c**, and **7e**, respectively. In similar fashion the signal for the equatorial methylene substituent at C-1 in **7e** appears upfield (Δ 0.15 ppm) from its axial counterpart in **6e**. Previous observations[11] suggest that axial carboalkoxycyclohexanes should have shorter vpc retention times than their equatorial epimers. This relationship holds here for **6c** and **7c**, as well as for the homologous esters **6e** and **7e**.

One final matter deserves attention. A tentative stereochemical assignment has been made[12] for keto esters **19** and **20** on the basis of the data reproduced in Table I. In view of our present results and earlier work cited above it appears that isomer A should be considered to be **19**, and isomer B, **20**. This is the reverse of the original conclusion.



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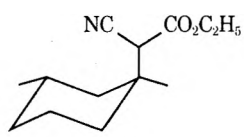

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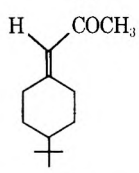

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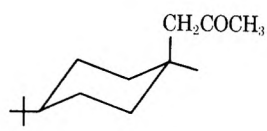

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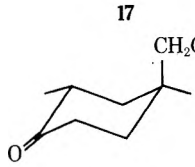

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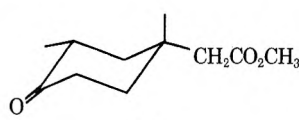

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TABLE I

NMR AND VPC DATA FOR 19 AND 20

Isomer	Chemical shift, δ: C-1 CH_3	Chemical shift, δ: C-1 CH_2	Vpc retention time, min
A	1.08	2.58	29.3
B	1.32	2.24	34.7

Experimental Section

Materials and Equipment.—All vpc was carried out using a Varian Aerograph Model 700 Autoprep or Model A-90-P3 with a 10 ft × 0.375 in. column prepared using 45–60 Chromosorb W in aluminum tubing and one of the following: A, 30% DEGS; B, 30% SE-30; C, 30% Carbowax 20M; D, 30% Carbowax 1500. Unless otherwise noted, the column oven was operated at 145–160°, and the helium carrier gas flow rate was 120–135 ml/min. Ir and nmr spectra were obtained for CCl_4 solutions, the former on a Perkin-Elmer Model 237B spectrophotometer and the latter on a Varian A-60 (60 MHz) or HR-220 (220 MHz) spectrometer. Solutions were dried over $MgSO_4$ or Na_2SO_4; melting points are corrected; boiling points are uncorrected. Compounds purified by vpc were obtained as colorless oils. Photochemical experiments were carried out with a Hanovia Model L mercury lamp (no. 679A-36) in a quartz immersion well using Pyrex 7740 as filter.

***trans*- and *cis*-1,3-Dimethylcyclohexanecarbonitrile (6a and 7a).**—3-Methylcyclohexanecarbonitrile (**5**, 4.496 g, 36.5 mmol)[2] was alkylated according to the procedure of House.[3] Distillation afforded a mixture of isomers (4.458 g, 89%), which were separated on a preparative scale on column A to give first **6a** (70% of the mixture): ir 2890 (m), 2930 (s), 2876 (m), 2850 (m), 2230 (w), 1460 (s), 1375 (w), 1118 (w), 960 (w), 940 cm^{-1} (w); nmr (60 MHz) δ 2.28–0.50 (br m), 1.32 (s, CH_3), 0.94 (d, CH_3).

Anal. Calcd for $C_9H_{15}N$: C, 78.77; H, 11.02; N, 10.21. Found: C, 78.42; H, 11.11; N, 10.12.

The second product was **7a** (30% of the mixture): ir 2930 (s), 2870 (m), 2235 (w), 1460 (s), 1450 (m), 1435 (m), 1375 cm^{-1} (m); nmr (60 MHz) δ 2.30–0.78 (br m), 1.36 (s, CH_3), 0.94 (br d, CH_3).

Anal. Calcd for $C_9H_{15}N$: C, 78.77; H, 11.02; N, 10.21. Found: C, 78.85; H, 11.10; N, 10.22.

***trans*-1,3-Dimethylcyclohexanecarboxylic Acid (6b).**—The major nitrile (250 mg), ethylene glycol (10 ml), potassium hydroxide (3 g), and water (2 ml) were heated at reflux for 3 days. The reaction mixture was cooled, poured into water, and extracted with ether. Acidification of the aqueous phase, extraction with ether, drying, and removal of solvent *in vacuo* gave 247 mg (87%) of crystalline material, mp 86–87.5°. Recrystallization from aqueous methanol gave material of mp 88.5–89.5°, unchanged on further recrystallization (lit.[1] mp 90°): ir 3450–2400 (br), 2950 (m), 2930 (s), 2870 (m), 2850 (m), 1700 (s), 1465 (m), 1450 (m), 1250 (m), 1230 (m), 1175 cm^{-1} (m); nmr (220 MHz) δ 12.03 (br s, 1 H), 2.22–2.04 (m, 2 H), 1.72–1.30 (m, 4 H), 1.20 (s, 3 H), 1.05–0.64 (m, 3 H), 0.88 (d, J = 7 Hz, 3 H).

***cis*-1,3-Dimethylcyclohexanecarboxylic acid (7b)** was prepared in 92% yield from **7a** as described above for **6b**. The crude product was a slightly yellow oil which slowly crystallized, mp 40–42.5°. Recrystallization from aqueous methanol gave material of mp 45–46° (lit.[1] mp 44°): ir 3400–2400 (br), 2955 (m), 2935 (m), 2870 (m), 1700 (s), 1468 (m), 1295 (m), 1270 (m), 1168 cm^{-1} (w); nmr (220 MHz) δ 11.54 (br s, 1 H), 2.00–1.20 (br m, 8 H), 1.22 (s, 3 H), 0.95–0.73 (m, with d at 0.89, J = 7 Hz, 4 H).

Arndt–Eistert Synthesis with 6b.—A mixture of the acid (2.73 g, 0.0175 mol) and thionyl chloride (10 ml) was stirred at room temperature overnight. After heating to reflux for 1 hr, bulb-to-bulb distillation gave 2.95 g, bp 120° (14 mm), of acyl chloride. This was immediately taken up in ether and added to a large

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(12) W. F. Erman and T. W. Gibson, *Tetrahedron*, **25**, 2493 (1969).

excess of ethereal diazomethane (~0.06 mol). The mixture was left standing in an ice bath overnight. Removal of the ether afforded 3.14 g of a yellow oil; ir analysis indicated that the diazo ketone had been formed (2100 cm^{-1}), but that some acid chloride remained. Wolff rearrangement of this crude diazo ketone in methanol with silver benzoate catalysis[6] gave, after work-up and bulb-to-bulb distillation, 2.18 g of a colorless oil. Vpc analysis on column A indicated four components in the ratio 1.3:2.2:2.3:1. The first was **6c**, having a retention time identical with that of an authentic sample prepared from **6b** and diazomethane. The second component was identified as 1,5-dimethylbicyclo[3.2.1]-octan-6-one (**11**): ir 2955 (m), 2935 (m), 2875 (m), 2852 (m), 1745 (s), 1450 (m), 1398 (m), 1345 (m), 1250 (m), 1100 (m), 1082 (m), 950 cm^{-1} (w); nmr (220 MHz) δ 2.01 (dd, J = 18, 4 Hz, 1 H), 1.85 (d, J = 18 Hz, 1 H), 1.73–1.18 (br m, 8 H), 1.12 (s, 3 H), 0.95 (s, 3 H).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.79; H, 10.57.

The third component was identified as *trans*-1,3-dimethylcyclohexaneacetic acid methyl ester (**6e**): ir 2950 (m), 2925 (m), 2870 (m), 2845 (m), 1745 (s), 1450 (m), 1250 (m), 1195 (m), 1005 cm^{-1} (m); nmr (220 MHz) δ 3.57 (s, 3 H), 2.21 (s, 2 H), 1.74–0.65 (br m with s at 0.96 and d at 0.84, J = 7 Hz, 15 H).

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.90. Found: C, 71.85; H, 11.13.

The fourth component was identified as *exo*-1,3-dimethylbicyclo[3.2.1]octan-7-one: ir 2955 (m), 2930 (m), 2870 (m), 1745 (s), 1450 (m), 1400 (m), 1370 (m), 1115 (m), 1032 (m) cm^{-1}; nmr (220 MHz) δ 2.47 (br s, 1 H), 2.15 (dd, J = 18, 7 Hz, 1 H), 2.00 (ddd, J = 18, 4, ~1 Hz, 1 H), 1.79–0.96 (br m, 7 H), 0.94 (s, 3 H), 0.89 (d, J = 6 Hz, 3 H).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.96; H, 10.50.

Arndt–Eistert Synthesis with 7b.—Similar treatment of acid **7b** (317 mg), but without distillation of the intermediate acid chloride, gave after work-up of the rearrangement product 314 mg, which was analyzed on column D. The major component (~95% of volatile material) was collected and identified as *cis*-1,3-dimethylcyclohexaneacetic acid methyl ester (**7e**): ir 2950 (m), 2930 (m), 2865 (m), 2845 (m), 1742 (s), 1450 (m), 1432 (m), 1427 (m), 1145 (m), 1130 (m), 1115 (m), 1000 cm^{-1} (w); nmr (220 MHz) δ 3.56 (s, 3 H), 2.06 (s, 2 H), 1.77–0.69 (br m with s at 0.98 and d at 0.85, J = 6 Hz, 15 H).

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.86; H, 10.95.

***trans*-1,3-Dimethylcyclohexaneacetic Acid Methyl Ester from 3-Methylcyclohexanone.**—A mixture of 3-methylcyclohexanone (6.74 g, 0.06 mol), ethyl cyanoacetate (6.79 g, 0.06 mol), acetic acid (720 mg), ammonium acetate (480 mg), and benzene (21 ml) was heated at reflux for 4.5 hr with continuous removal of water with a Dean–Stark trap. The reaction mixture was cooled, poured into water, and extracted with ether; the combined organic phases were washed with saturated sodium bicarbonate and brine and dried. After removal of ether *in vacuo*, distillation afforded 8.79 g (71%) of a colorless oil considered to be **15**: bp 115–116° (0.5 mm); ir 2940 (m), 2225 (w), 1727 (s), 1602 (s), 1280 (m), 1255 (m), 1215 (s), 1198 (m), 1095 (m), 1038 (m), 945 (w), 850 cm^{-1} (w); the nmr spectrum indicated a mixture of isomers.

To a solution of methylmagnesium iodide [prepared from magnesium (558 mg, 0.023 g-atom) and iodomethane (3.12 g, 0.022 mol) in 15 ml of ether] was added a solution of tetrakisiodo-(tri-*n*-butylphosphine)copper (394 mg, 0.001 mol) in 10 ml of ether and, immediately afterwards, a solution of the unsaturated cyano ester **15** (2.07 g, 0.01 mol) in 10 ml of ether at a rate that caused refluxing of the solvent. Immediately after completion of the addition, the reaction mixture was poured into saturated ammonium chloride. After extraction with ether, drying, and removal of solvent, 2.47 g of colorless oil was obtained. This material, considered to be **16**, was purified on column B (208°): ir 2930 (m), 2245 (w), 1747 (s), 1450 (m), 1235 (m), 1170 (m), 1023 cm^{-1} (m); nmr (60 MHz) δ 4.33 (q, J = 7 Hz, 2 H), 3.83 (s, 1 H), 2.25–0.55 [br m with t at 1.38, J = 7 Hz, s at 1.13, and d at 0.97 and d at 0.90 (due to diastereomers), 18 H].

The crude cyano ester **16** was hydrolyzed with potassium hydroxide (5.0 g) in ethylene glycol (15 ml) containing 3 ml of water for 15 hr. The reaction mixture was cooled, poured into water, and extracted with ether; the aqueous phase was acidified with concentrated hydrochloric acid and extracted with ether. The combined organic extracts were washed with brine, dried, and evaporated *in vacuo* to yield a pale yellow oil which was heated to 205° for 0.75 hr. The reaction mixture was cooled, diluted with ether, and extracted with 5% aqueous sodium carbonate; the basic extracts were acidified, extracted with ether, and dried over magnesium sulfate. The ethereal filtrate was treated with diazomethane. After removal of solvent *in vacuo*, the residue (1.395 g, 76% from **15**) was analyzed by vpc on column C. One component was detected; this had an identical ir spectrum and vpc retention time with those of **7e** prepared by Arndt–Eistert homologation of **7b**.

Photolysis of 1,5-Dimethylbicyclo[3.2.1]octan-6-one.—A solution of ketone **11** (60 mg) in benzene (50 ml) was irradiated through Pyrex. Ir spectroscopy was used to monitor the disappearance of starting material and appearance of a ketone band at 2108 cm^{-1}; essentially no ketone remained after 8.25 hr. The photolysate was allowed to stand overnight with 3.0 ml of absolute methanol. After removal of solvents by distillation, vpc analysis on column B indicated two major components. The first was presumed to be 1,3-dimethylcyclohex-2-eneacetaldehyde (~40%) from the following data: ir 2930 (m), 2875 (m), 2840 (w), 2730 (w), 1722 (s), 1450 (m), 1375 (m), 855 (w), 825 cm^{-1} (w); nmr (220 MHz) δ 9.72 (t, J = 3 Hz, 1 H), 5.24 (br s, 1 H), 2.20 (t, J = 3 Hz, 2 H), 1.93–1.81 (m, 2 H), 1.71–1.33 (m, 4 H), 1.63 (d, $J \cong$ 1 Hz, 3 H), 1.07 (s, 3 H). The second component (~60%) was **6e**, having ir and nmr (220 MHz) spectra and vpc retention time identical with those of the independently synthesized material described above.

***trans*-1,3-Dimethylcyclohexanecarboxylic Acid Methyl Ester (6c).**—Acid **6b** was esterified with etheral diazomethane and the product was purified on column C: ir 2955 (s), 2940 (s), 2875 (m), 2845 (m), 1740 (s), 1455 (m), 1220 (m), 1200 (m), 1150 (s), 1125 cm^{-1} (m); nmr (220 MHz) δ 3.60 (s, 3 H), 2.17–2.02 (m, 2 H), 1.67–0.52 (br m with s at 1.09 and d at 0.86, J = 6 Hz, 13 H).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.53; H, 10.67.

***cis*-1,3-Dimethylcyclohexanecarboxylic Acid Methyl Ester (7c).**—This was prepared just as **6c** above: ir 2955 (s), 2860 (m), 1738 (s), 1462 (m), 1427 (m), 1245 (s), 1200 (m), 1110 cm^{-1} (s); nmr (220 MHz) δ 3.59 (s, 3 H), 1.72–1.12 (br m, 8 H), 1.17 (s, 3 H), 0.88 (d, J = 6 Hz, with m at ~0.85, 4 H).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.58; H, 10.72.

Registry No.—**5**, 38857-62-4; **6a**, 38864-01-6; **6b**, 38864-02-7; **6b** acid chloride, 38864-03-8; **6c**, 38864-04-9; **6d**, 38864-05-0; **6e**, 38864-06-1; **7a**, 38864-07-2; **7b**, 38864-08-3; **7c**, 38864-09-4; **7e**, 38864-10-7; **11**, 38857-63-5; **12**, 38857-64-6; **13**, 38857-65-7; **15**, 38857-66-8; **16**, 38857-67-9; 3-methylcyclohexanone, 591-24-2; ethyl cyanoacetate, 105-56-6.

Acknowledgments.—We thank Mr. S. T. Bella for microanalyses and Miss Luz Catan for expert technical assistance. Nmr spectra (220 MHz) were obtained on an instrument at The Rockefeller University and operated by a consortium supported in part by NSF Grant No. GB-12278 and grants from Research Corporation and the Alfred P. Sloan Foundation.

anti-Tricyclo[3.1.0.0^{2,4}]hexanes. Synthesis and Reactions

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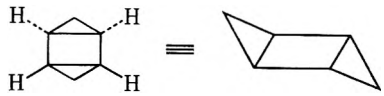
Received November 6, 1972

A facile synthesis of dimethyl *anti*-tricyclo[3.1.0.0^{2,4}]hexane-1,2-dicarboxylate (**4**) involving two intramolecular nucleophilic displacements is described. Thermolysis of **4** gives dimethyl cyclohexa-1,4-diene-1,2-dicarboxylate (**7**). Silver ion catalyzed reaction of 1,2-bis(acetoxymethyl)-*anti*-tricyclo[3.1.0.0^{2,4}]hexane (**8**) also results in ring opening, giving 1,2-bis(acetoxymethyl)cyclohexa-1,4-diene (**10**) and 2-acetoxymethyltoluene (**11**). Catalytic hydrogenation of **4** proceeds stereospecifically from an endo face, giving a product shown to be dimethyl bicyclo[3.1.0]hexane-1,*endo*-2-dicarboxylate (**17**). The addition of hydrogen bromide to **4** yields a pair of products shown to be the epimeric bicyclo[3.1.0]hexanes **20** and **21**, in accord with expectations for stereospecific attack of bromide ion on protonated **4**.

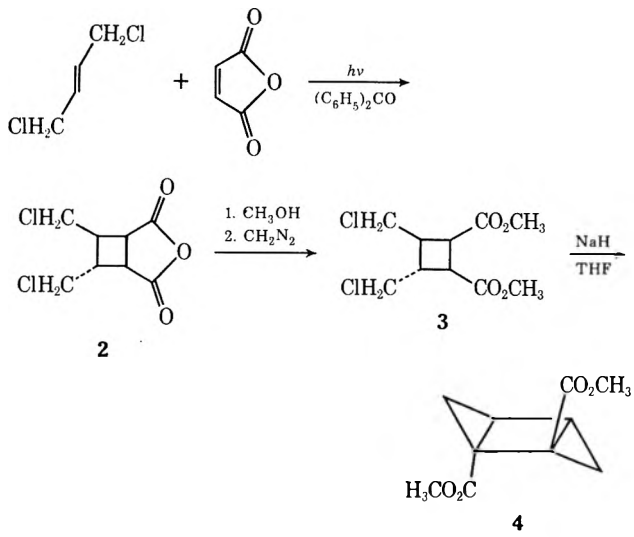
Although *anti*-tricyclo[3.1.0.0^{2,4}]hexane (**1**) and a few of its derivatives have been described, little chemistry of this interesting strained ring system has been studied; only hydrogenation and thermolysis of the parent hydrocarbon[2] and thermolysis of various derivatives[3-5] have been reported. We would like to report a new, convenient synthesis of this ring system and to describe some of its thermal, catalytic, and ionic reactions.



1

Synthesis.—Previous syntheses of substituted *anti*-tricyclo[3.1.0.0^{2,4}]hexanes have relied on photochemical[4-7] or metal-catalyzed[3] dimerizations of cyclopropenes. The method which we have used provides much easier access to these compounds, as outlined in Scheme I. The benzophenone-sensitized photoaddition of maleic anhydride to *trans*-1,4-dichloro-2-butene afforded anhydride **2** in 76% yield (ν_{CO}^{KBr} 1865, 1800 cm^{-1}). The reaction of **2** first with methanol and then with diazomethane furnished the bis methyl ester **3** in 91% yield (ν_{CO}^{neat} 1740 cm^{-1}). The nmr spectrum of **3** confirmed the trans arrangement of the chloromethyl substituents. (Methoxyl resonances appeared at δ 3.65 and 3.70.) Refluxing a solution of **3** in tetrahydrofuran with an excess of sodium hydride produced dimethyl *anti*-tricyclo[3.1.0.0^{2,4}]hexane-1.2-dicarboxylate (**4**) in 59% yield.

SCHEME I



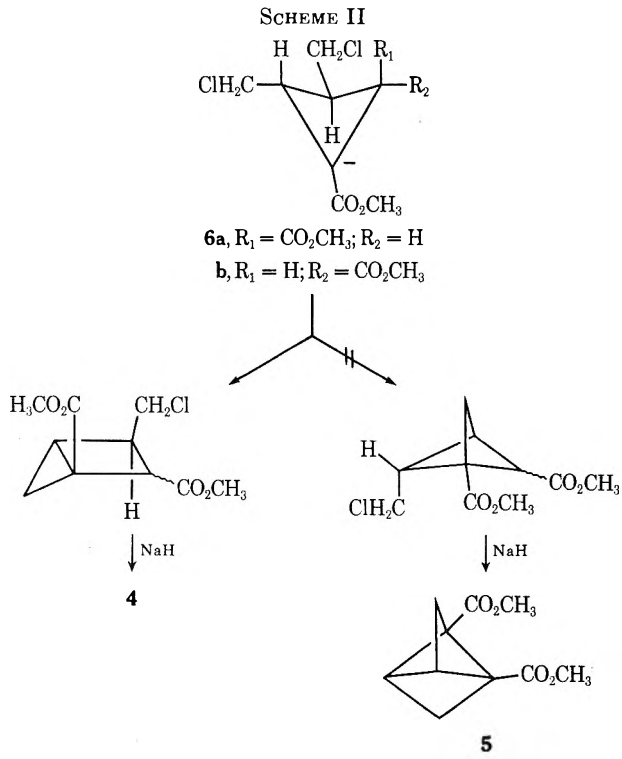
2 **3** **4**

The structure of **4** was established on the basis of its spectral and chemical properties. Its mass spectrum showed a molecular ion at *m/e* 196 ($C_{10}H_{12}O_4$). The pmr spectrum showed no olefinic absorption; a single methoxyl absorption (6 H) appeared at δ 3.67; and three separated multiplets (2 H each) were found at δ 1.72, 1.95, and 2.20. While a detailed assignment of these absorptions was not attempted, they are clearly compatible with the structure proposed. The cmr spectrum of **4** (parts per million downfield from external TMS) showed, besides absorptions at 71.73 and 52.96 for the carbonyl and methyl carbons, three absorptions at 29.41, 31.09, and 32.66 assigned, respectively, to the quaternary, tertiary, and secondary carbon atoms on the basis of the ^{13}C–H coupling patterns. The fact that the bridgehead carbon atoms absorb at higher field than the bridge carbon atoms may be ascribed to these nuclei lying in the shielding region of the adjacent cyclopropane ring. The values obtained for the ^{13}C–H coupling constants ($J_{^{13}C-H}$ = 188 Hz, $J_{^{13}C-H_2}$ = 166 Hz) are in the range expected for a strained molecule of this type and are indicative of the high degree of *s* character associated with the bonds in this system.[8]

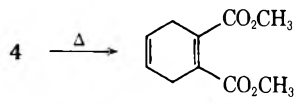
It is of interest that the dehydrohalogenation of **3** gives **4**, the result of two 1,3-intramolecular displacements, rather than **5**, the product which would have resulted from two 1,4 displacements. This preference may be rationalized on the basis of the relative activation energies expected for the initial displacements in carbanions **6a** and **6b**. These displacements can yield either a bicyclo[2.1.0]pentane, which should cyclize readily to **4**, or a bicyclo[1.1.1]pentane, which could cyclize to **5** (Scheme II). Insofar as the activation energies of these two displacements reflect the strain energies of the bicyclic products, we would expect to obtain the observed product **4**, since it has been calculated that bicyclo[1.1.1]pentane is more highly strained than bicyclo[2.1.0]pentane.[9]

(1) National Institutes of Health Postdoctoral Fellow, 1972.
(2) E. L. Allred and J. C. Hinshaw, *J. Amer. Chem. Soc.*, **90**, 6885 (1968).
(3) F. J. Weigert, R. L. Baird, and J. R. Shaply, *J. Amer. Chem. Soc.*, **92**, 6630 (1970).
(4) H. H. Stechl, *Chem. Ber.*, **97**, 2681 (1964).
(5) C. Deboer and R. Breslow, *Tetrahedron Lett.*, 1033 (1967).
(6) N. Obata and I. Moritani, *Bull. Chem. Soc. Jap.*, **39**, 2250 (1966).
(7) J. Trotter, C. S. Gibbons, N. Nakatsuka, and S. Masamune, *J. Amer. Chem. Soc.*, **89**, 2792 (1967).
(8) K. B. Wiberg, *Advan. Alicyclic Chem.*, **3**, 193 (1968).
(9) N. C. Baird, *Tetrahedron*, **26**, 2185 (1970).

SCHEME II

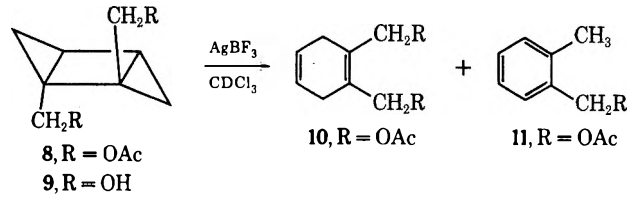


Thermolysis.—A sample of **4** maintained at 190° in an evacuated glass tube for 1.5 hr was quantitatively converted to dimethyl cyclohexa-1,4-diene-1,2-dicarboxylate (**7**), identified by comparison with an authentic



sample.[10] Although this isomerization is formally a $-[2_a + 2_a]$ cycloaddition, which, on the basis of orbital symmetry concepts, is not allowed,[11] whether this reaction is concerted or proceeds through a discrete diradical intermediate is, as yet, unanswered.[12]

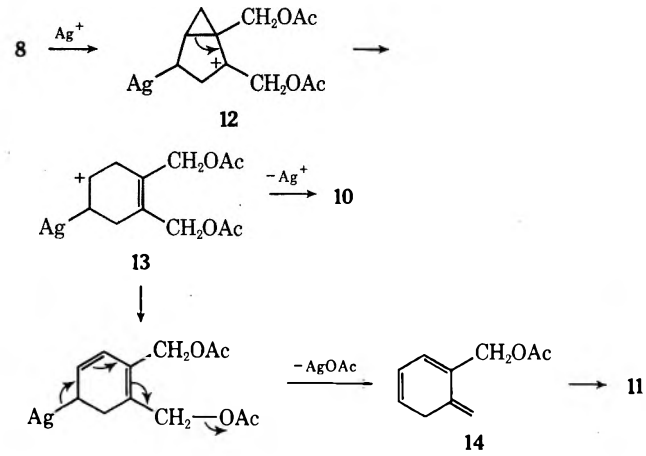
Silver-Catalyzed Rearrangement.—In view of the current interest shown in silver-catalyzed rearrangements of strained hydrocarbons,[13] we have examined the silver-catalyzed rearrangement of **4**. When a sample of **4** was refluxed in chloroform in the presence of silver fluoroborate, it was recovered unchanged. We noted that Eaton, *et al.*,[14] in their study of the silver-catalyzed rearrangement of the cubyl system, observed a rate-retarding effect by carbomethoxy groups. Consequently, we prepared the diacetate **8** (by reduction of **4** with lithium aluminum hydride to give diol **9**, followed by acetylation) with the expectation that the absence of the electron-withdrawing substituents would make reaction more likely. When a sample of **8** in chloroform-*d* containing a catalytic quantity of silver fluoroborate was heated to boiling for 1 min and allowed to stand at room temperature for 1 hr, the nmr spectrum of the resulting solution indicated a complete conversion of **8** to **10** (84%) and **11** (16%).[15]



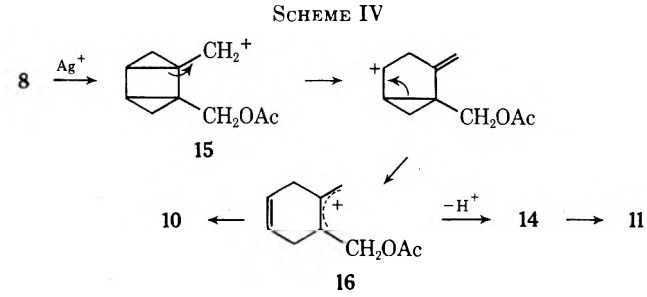
The structure of **10** was proven by independent synthesis (see Experimental Section); the minor product (**11**) was identical with the compound obtained upon acetylation of 2-hydroxymethyltoluene.[16]

With the experimental data obtained thus far, either of two mechanisms for the formation of **10** and **11** appear plausible; these are shown in Schemes III and IV.

SCHEME III



SCHEME IV



In Scheme III, silver ion adds across one of the strained σ bonds of **8** to produce the carbonium ion **12**, subsequent rearrangement of which (to **13**), followed by loss of silver ion, would give **10**. Loss of a proton from **13**, followed by loss of silver acetate as shown, would produce **14**. Tautomerization of **14** to give **11** would follow.

Scheme IV involves a silver ion assisted ionization of **8**[17] to give carbonium ion **15**, subsequent rearrangement of which would yield the allylic carbonium ion **16**. Recapture of acetate would yield **10**, while loss

(10) O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, **490**, 236 (1931).

(11) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1969, p 70.

(12) On the basis of a measurement of the activation energy for the thermal rearrangement of the parent hydrocarbon, it has recently been suggested that this reaction might be concerted: J. E. Baldwin and J. Ollerenshaw, *Tetrahedron Lett.*, 3757 (1972).

(13) For a leading reference, see R. J. Roth and T. J. Katz, *J. Amer. Chem. Soc.*, **94**, 4770 (1972).

(14) L. Cassar, P. E. Eaton, and J. Halpern, *J. Amer. Chem. Soc.*, **92**, 6366 (1970).

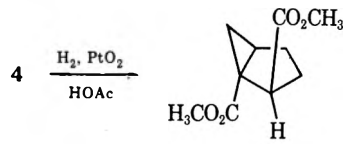
(15) That **11** is a primary product, and not simply the result of acetic acid elimination from **10**, was demonstrated by the observation that **10** was unchanged when subjected to the reaction conditions for a 24-hr period.

(16) G. H. Daub and R. N. Castle, *J. Org. Chem.*, **19**, 1571 (1954).

(17) Silver ion assisted ionization of some strained methyl ethers has recently been observed: L. A. Paquette and G. Zon, *J. Amer. Chem. Soc.*, **94**, 5096 (1972).

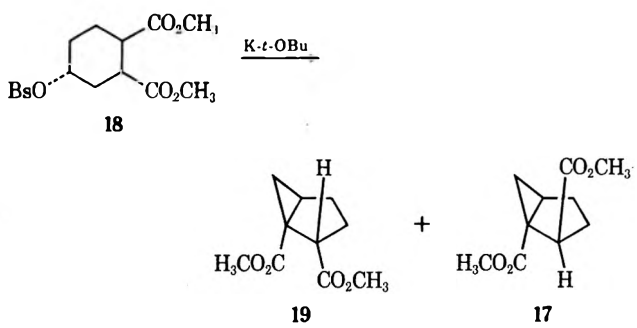
of a proton would give **14**. Tautomerization of **14** again completes the sequence.[18]

Hydrogenation.—Hydrogenation of the parent hydrocarbon **1** with platinum oxide in acetic acid at atmospheric pressure is reported[2] to yield cyclohexane and methylcyclopentane. In contrast to these results, hydrogenation of **4** under identical conditions proceeded with cleavage of a single bridging bond, giving dimethyl bicyclo[3.1.0]hexane-1,*endo*-2-dicarboxylate (**17**) stereospecifically within the limits of nmr detection.



17

To assign the stereochemistry of **17**, we prepared brosylate **18** from the corresponding alcohol of known configuration,[19] with the expectation that a base-induced intramolecular displacement of the brosylate group would give dimethyl bicyclo[3.1.0]hexane-1,*exo*-2-dicarboxylate (**19**) as the major isomer, provided that conditions could be found which would minimize subsequent epimerization of **19**. This could be accomplished by the addition of potassium *tert*-butoxide to a solution of **18** in *tert*-butyl alcohol at room temperature, giving **19** and **17** in a 3:2 ratio.[20] That this ratio of products is not simply the equilibrium ratio was demonstrated by equilibration studies using sodium methoxide in methanol; an equilibrium mixture consisting of 78% **17** and 22% **19** was obtained. The above results indicate that the reaction of **18** with

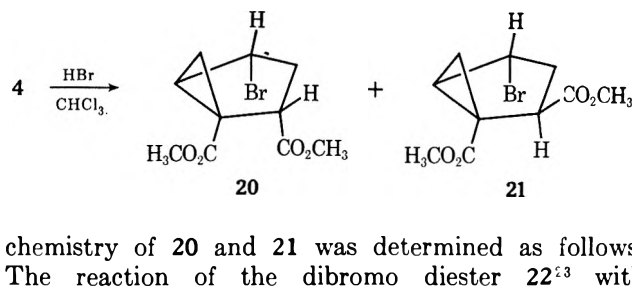


18 **19** **17**

base gave **19** as the initial product. It follows that **19** has the exo configuration and that **17** is the corresponding endo epimer. These assignments were substantiated by the nmr spectra of **17** and **19**. While **17** showed a multiplet in the region of δ 3.33–3.60 for the proton α to the carboxylate group, **19** showed the corresponding absorption at 2.95–3.17. It is well established that, for 2-substituted bicyclo[3.1.0]hexanes, the proton α to the substituent absorbs at higher field when the substituent is exo, owing to the shielding properties of the cyclopropyl ring.[21]

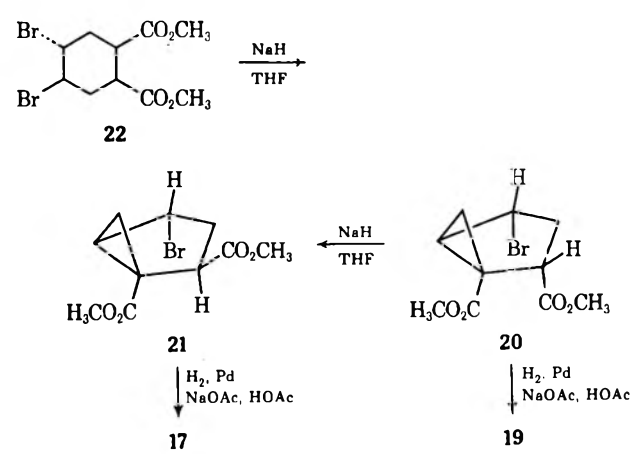
The most striking feature of the hydrogenation of **4** is its stereospecificity. This requires that the hydrogen must have added from the inside of one of the "flaps" of the *anti*-tricyclo[3.1.0.0^{2,4}]hexane skeleton. In this respect, the reaction bears a formal similarity to the cycloadditions described by Gassman,[22] in which bicyclo[2.1.0]pentane suffers attack from the concave face.

Hydrobromination.—When **4** is allowed to stand in a chloroform solution of hydrogen bromide for 30 min, it is completely converted to a mixture of dimethyl *exo*-4-bromobicyclo[3.1.0]hexane-1,*exo*-2-dicarboxylate (**20**, 44%) and dimethyl *exo*-4-bromobicyclo-[3.1.0]-hexane-1,*endo*-2-dicarboxylate (**21**, 56%). The stereochemistry of **20** and **21** was determined as follows. The reaction of the dibromo diester **22**[23] with sodium hydride in tetrahydrofuran gave a 65% yield of a product identical with the major product obtained in the reaction of **4** with hydrogen bromide. Since the bromine atoms of **22** are trans to each other, the bromine substituent in **21**, obtained by this intramolecular nucleophilic displacement, must then be exo to the three-membered ring. The endo configuration of the ester group in **21** was demonstrated by hydrogenolysis of **21** to give **17**. When a sample of **20** was allowed to react with sodium hydride in tetrahydrofuran, it was epimerized to **21**, along with small amounts of dimethyl phthalate and an unidentified product. It therefore can be concluded that the bromine atom of **20** is also exo. The exo configuration of the ester group of **20** was confirmed by hydrogenolysis to give **19** (Scheme V).



20 **21**

SCHEME V



(18) An attempt has been made to distinguish between the mechanisms presented in Schemes III and IV by conducting the reaction in acetic acid-d_4. However, under these conditions the reaction proceeded much more slowly, and **10** and **11** were no longer the major products, but were accompanied by at least four additional components. Since it is likely that a different mechanism is operating in acetic acid, any attempt to extrapolate the information obtained under these conditions to the reaction conducted in chloroform would be unreliable.

(19) J. Klein, E. Dunkelblum, and D. Avrahami, *J. Org. Chem.*, **32**, 935 (1967).

(20) This reaction is a direct extension of the bicyclo[3.1.0]hexane synthesis developed by N. A. Nelson and G. A. Mortimer, *J. Org. Chem.*, **22**, 1146 (1957).

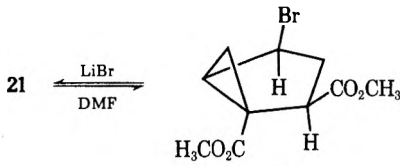
(21) C. D. Poulter, R. S. Borkess, J. I. Brauman, and S. Winstein, *J. Amer. Chem. Soc.*, **94**, 2291 (1972).

(22) P. G. Gassman, K. T. Mansfield, and T. J. Murphy, *J. Amer. Chem. Soc.*, **91**, 1684 (1969).

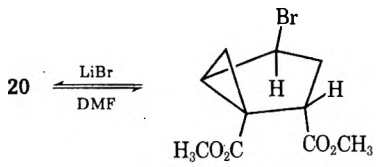
(23) U. F. Kucherov, A. L. Shabanov, and A. S. Onishchenko, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 884 (1963).

To gain further insight into the hydrobromination of **4**, we performed several other experiments. It was found that, when both **20** and **21** were resubmitted to the reaction conditions, they were recovered unchanged. When a sample of **4** was allowed to react with deuterium bromide in chloroform, the nmr spectra of the isolated products showed that the absorptions at δ 3.20 and 3.83, assigned to the protons α to the carboxylate group in **20** and **21**, were absent; no other deuterium incorporation in either isomer was apparent.

To determine whether the reaction of **4** with hydrogen bromide is thermodynamically or kinetically controlled, equilibration studies were conducted with **20** and **21**. A sample of **21** treated with lithium bromide in dimethylformamide gave an equilibrium mixture consisting of **21** (56%) and the new epimer **23**



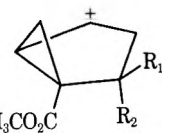
23



24

(44%), as determined from the nmr spectrum of the mixture. Similarly, treatment of **20** with lithium bromide in dimethylformamide gave an equilibrium mixture consisting of **20** (20%) and **24** (80%). These results clearly indicate that the reaction of **4** with hydrogen bromide is kinetically controlled, since epimers **23** and **24** are not observed.

An important feature of the hydrobromination of **4** is the stereochemistry of the resulting bicyclo[3.1.0]-hexanes, **20** and **21**. While there is essentially no stereochemical preference shown for the carboxylate group in the products, the reaction is stereospecific with respect to the bromine substituents. One of the first mechanisms which we considered involves addition of a proton to a strained bridgehead bond, giving the bicyclo[3.1.0]hexyl cations **25** and **26**. Stereo-



25, $R_1 = CO_2CH_3$; $R_2 = H$
26, $R_1 = H$; $R_2 = CO_2CH_3$

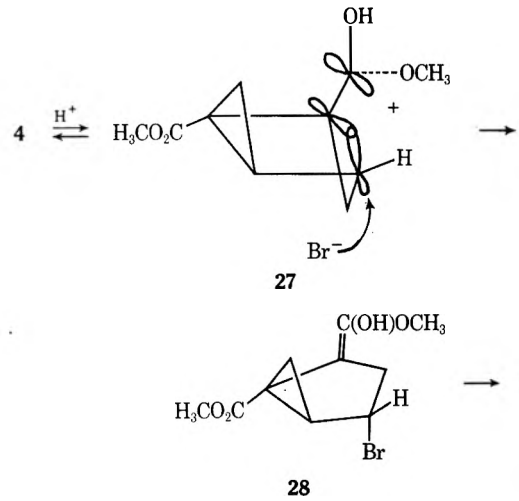
specific (exo) addition of bromide ion would give the observed products. However, it appears that, when the 2-bicyclo[3.1.0]hexyl cation has been generated under a variety of conditions, addition of a nucleophile to the cation is generally not stereospecific.[24]

(24) (a) K. B. Wiberg, R. A. Fenoglio, U. Z. Williams, and R. W. Obersax, *J. Amer. Chem. Soc.*, **92**, 568 (1970); (b) E. C. Friedrich and M. A. Saleh, *Tetrahedron Lett.*, 1373 (1971); (c) P. R. Brook, R. M. Ellam, and A. S. Bloss, *Chem. Commun.*, 425 (1968); (d) G. H. Schmid and A. Brown, *Tetrahedron Lett.*, 4695 (1968); (e) R. N. McDonald and G. E. Davis, *J. Amer. Chem. Soc.*, **94**, 5078 (1972).

Consequently, it is unlikely that **25** and **26** are intermediates in the hydrobromination of **4**.

The mechanism shown in Scheme VI appears to offer the best explanation of the experimental results.

SCHEME VI



In this scheme, protonation of **4** occurs at an ester carbonyl oxygen, giving cation **27**. Attack of bromide ion at the back lobe of the appropriate σ orbital would yield enolized ester **28**, tautomerization of which to the observed products would follow. The specificity of attack by bromide ion and the formation of both epimers at the ester site are thereby simply accommodated.

Experimental Section

trans-**1,2-Bis(chloromethyl)cyclobutane-*cis*-3,4-dicarboxylic Acid Anhydride (2).**—A solution of 30.0 g (0.306 mol) of maleic anhydride and 14.0 g (0.077 mol) of benzophenone in 370 ml of *trans*-1,4-dichloro-2-butene was placed in a photochemical apparatus equipped with a 450-W Hanovia lamp, Pyrex filter, and a water-cooled quartz immersion well. The reaction mixture was flushed with nitrogen for 8 min. The mixture was irradiated with stirring for 48 hr, at which time a white solid began to separate. The unreacted *trans*-1,4-dichloro-2-butene was removed by distillation [35° (4 mm); this material can be used in further runs without additional purification]. The residue was refluxed with 300 ml of hexane for ~15 min. The hot hexane solution was decanted and discarded. The mixture was then stirred at reflux in 250 ml of ether. The mixture was allowed to cool to room temperature. An off-white solid (51.6 g, 76%) was collected by filtration. An analytical sample was prepared by dissolving the anhydride in hot chloroform and adding ether until the solution became cloudy. Cooling to room temperature gave colorless crystals of the anhydride **2**: mp 121–123.5°; ν_{max}^{KBr} 3020, 2960, 1865, 1800 cm^{-1}; nmr $\delta_{TMS}^{acetone\text{-}d_6}$ 2.90–4.05 (series of multiplets).

Anal. Calcd for $C_8H_8O_3Cl_2$: C, 43.07; H, 3.62; Cl, 31.79. Found: C, 42.98; H, 3.44; Cl, 31.61.

Dimethyl *trans*-1,2-Bis(chloromethyl)cyclobutane-*cis*-3,4-dicarboxylate (3).—To 90 ml of methanol was added 5.5 g (0.0246 mol) of **2**. The mixture was heated on a steam bath until it became homogeneous (~15 min). The solution was cooled to 0° and an ethereal solution of diazomethane was slowly added until a permanent yellow color remained. Excess diazomethane was destroyed by the addition of a few drops of acetic acid. The solvent was removed by rotary evaporation. The residue was distilled [156.5–157.5° (4 mm)] to give 5.98 g (91%) of **3**. After standing several weeks in the freezer, this material crystallized: mp 37–39°; ν_{max}^{neat} 2985, 2950, 1740 cm^{-1}; *m/e* 237 (M − OCH_3), 209 (M − $COOCH_3$); nmr $\delta_{TMS}^{acetone\text{-}d_6}$ 3.77–3.93 (m, 4 H), 2.65–3.55 (m, 4 H), 3.65 (s, 3 H, CH_3), 3.70 (s, 3 H, CH_3).

Anal. Calcd for $C_{10}H_{14}O_4Cl_2$: C, 44.63; H, 5.24; Cl, 26.35. Found: C, 44.47; H, 5.24; Cl, 26.16.

Dimethyl *anti*-Tricyclo[3.1.0.0^{2,4}]hexane-1,2-dicarboxylate (4).—A mixture of 8.0 g (0.0297 mol) of **3**, 1.65 g (0.0687 mol) of sodium hydride, and 1 drop of methanol was stirred at reflux in 170 ml of tetrahydrofuran (THF) for 48 hr. The mixture was filtered from the precipitated salts and the THF removed by rotary evaporation. The mixture was mixed with a saturated solution of ammonium chloride. The aqueous mixture was extracted with ether. The ether solution was dried over magnesium sulfate and treated with Norit. The ether was removed at reduced pressure. The residue was distilled. The fraction boiling at 77–79° (0.02 mm) was collected, and 3.45 g (59%) of **4** was obtained as a liquid which, on standing several hours, crystallized: mp 44–46°; ν_{max}^{neat} 3014, 3000, 1740, 1335, 1260, 1205, 1165, 1097, 770, 735, 717 cm^{-1}; cmr (neat, parts per million downfield from external TMS) 29.41 (CCOOCH$_3$), 31.09 (CH, $J_{^{13}C-H}$ = 188 Hz), 32.66 (CH$_2$, $J_{^{13}C-H}$ = 166 Hz), 52.96 (CH$_3$), 71.73 (CO); pmr $\delta_{TMS}^{CDCl_3}$ 1.72 (m, 2 H), 1.95 (m, 2 H), 2.20 (m, 2 H), 3.67 (s, 6 H, CH$_3$); uv $\lambda_{max}^{n\text{-heptane}}$ 227 mμ (ϵ 82.2); mass spectrum *m/e*, 196.

Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 60.96; H, 6.23.

Thermolysis of 4.—In a thick-walled glass tube was placed 0.075 g (0.446 mmol) of **4**. The tube was evacuated (0.05 mm) and sealed. The tube was heated to 190° for 1.5 hr. The contents of the tube were subjected to molecular distillation [bath temperature 70° (0.05 mm)] to give dimethyl cyclohexa-1,4-diene-1,2-dicarboxylate (**7**). This material was identified by comparing its nmr and ir spectra with those of an authentic sample.[10]

1,2-Bis(hydroxymethyl)-*anti*-tricyclo[3.1.0.0^{2,4}]hexane (9).—To a stirred slurry of 0.425 g (11.2 mmol) of lithium aluminum hydride in 10 ml of ether was added dropwise a solution of 1.0 g (5.1 mmol) of **4** in 10 ml of ether at such a rate as to maintain reflux. The mixture was stirred at room temperature for an additional 1 hr and 45 min. Excess reducing agent was destroyed by the dropwise addition of a saturated sodium sulfate solution. The mixture was filtered, and the salts were washed with additional ether. The combined ether solutions were dried ($MgSO_4$). The ether was removed at reduced pressure, leaving 0.68 g (95%) of **9**. An analytical sample was obtained *via* molecular distillation [bath temperature 80° (0.3 mm)]: ν_{max}^{neat} 3305, 3015, 2995, 2949, 2889, 2835, 1005 cm^{-1}; nmr $\delta_{TMS}^{CDCl_3}$ 3.59 [AB, 4 H, CH$_2$OH, $\Delta\nu_{AB}$ = 33.7 Hz, J_{AB} = −11.4 Hz (the low field portion of the AB pattern is further coupled, J = 1.0 Hz)], 4.16 (b s, 2 H, OH), 1.55 (m, 2 H), 1.33 (m, 2 H), 0.93 (m, 2 H).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 67.26; H, 8.70.

1,2-Bis(acetoxymethyl)-*anti*-tricyclo[3.1.0.0^{2,4}]hexane (8).—A solution of 0.30 g (2.1 mmol) of **9** and 0.075 g of sodium acetate in 2 ml of acetic anhydride was refluxed for 2 hr. The acetic anhydride was removed by distillation. The residue was mixed with water. Solid sodium bicarbonate was added until gas evolution ceased. The mixture was extracted with ether, and the ether solution was dried. The ether was removed by rotary evaporation. The residue was subjected to molecular distillation, giving 0.374 g (91%) of **8**. An analytical sample was isolated *via* preparative vpc (6 ft × 0.25 in. glass column, 5% Carbowax 20M on 60–80 mesh Chromosorb Q, 145°): ν_{max}^{neat} 3090, 2970, 2930, 2859, 1740 cm^{-1}; nmr $\delta_{TMS}^{CDCl_3}$ 2.16 (s, 6 H, CH$_3$), 4.33 (s, 4 H, CH$_2$OAc), 0.80–1.15 (m, 2 H), 1.32–1.76 (m, 4 H).

Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.32; H, 7.40.

Reaction of 8 with Silver Fluoroborate.—A solution of 0.240 g (1.25 mmol) of **8** in 1 ml of $CDCl_3$ was placed in an nmr tube. Several crystals of silver fluoroborate were added. The solution was heated to boiling on a steam bath for 1 min and allowed to stand at room temperature in the dark for 1 hr. At this time, the nmr spectrum of the dark brown solution showed the presence of **1,2-bis(acetoxymethyl)cyclohexa-1,4-diene (10, 84%)** and **2-acetoxymethyltoluene (11, 16%)**. The products were identified by comparison of their nmr spectra in the mixture and vpc retention times (5% Carbowax 20M on 60–80 mesh Chromosorb W, 150°) with independently prepared samples.

When a sample of **10** was subjected to the above reaction conditions for 24 hr, it was observed to be unchanged.

1,2-Bis(acetoxymethyl)cyclohexa-1,4-diene (10).—To a slurry of 0.68 g (17.9 mmol) of lithium aluminum hydride in 15 ml of ether was added with stirring 1.6 g (8.16 mmol) of dimethyl cyclohexa-1,4-diene-1,2-dicarboxylate (**7**)[10] in ether at such a rate as to maintain reflux. The mixture was stirred an additional 1 hr 45 min at room temperature. Excess reducing agent was destroyed by the dropwise addition of a saturated sodium sulfate solution. The mixture was filtered, and the ether was removed at reduced pressure. The residue was dissolved in 6 ml of acetic anhydride. To this solution was added 0.30 g of sodium acetate. The mixture was refluxed for 1 hr and 15 min. The excess acetic anhydride was removed by distillation, and the residue was mixed with water. Solid sodium bicarbonate was added until gas evolution ceased. The mixture was extracted with ether, and the ether solution was dried ($MgSO_4$) and treated with Norit. The ether was removed at reduced pressure, giving 1.16 g (74%) of a liquid which was distilled [98–100° (0.1 mm)]. Analysis by nmr of the distillate indicated that this material was **10** contaminated with 9% 1,2-bis(acetoxymethyl)benzene. An analytical sample of the diene was isolated *via* vpc (6 × 0.25 in. glass column, 5% Carbowax 20M on 60–80 mesh Chromosorb Q, 175°): mp 34–35°; ν_{max}^{neat} 3005, 2850, 2790, 1739, 1655, 1225 cm^{-1}; nmr $\delta_{TMS}^{CDCl_3}$ 2.14 (s, 6 H, CH$_3$), 2.87 (b s, 4 H, CH$_2$, $W_{1/2}$ = 3.0 Hz), 4.83 (s, 4, CH$_2$OAc), 5.90 (b s, 2 H, vinyl, $W_{1/2}$ = 2.7 Hz).

Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 63.91; H, 7.20.

Hydrogenation of 4.—A solution of 0.20 g (1.02 mmol) of **4** in 2 ml of acetic acid containing 0.06 g of platinum dioxide was hydrogenated at atmospheric pressure. Hydrogen uptake ceased after 1 hr. The mixture was filtered, poured into water, and extracted with ether. The ether solution was washed with a saturated solution of sodium bicarbonate and dried ($MgSO_4$). The ether was removed by rotary evaporation. The residue was subjected to molecular distillation [bath temperature 70° (0.05 mm)]; 0.180 g (92%) of dimethyl bicyclo[3.1.0]hexane-1,*endo*-2-dicarboxylate (**17**) was obtained. An analytical sample was isolated by preparative vpc (UCON nonpolar on 60–80 mesh Chromosorb W, 190°): ν_{max}^{neat} 2960, 2870, 1730 cm^{-1}; nmr $\delta_{TMS}^{CDCl_3}$ 1.14–2.12 (m, 7 H), 3.33–3.60 (m, 1 H, CHCOOCH$_3$), 3.67 (s, 3 H, CH$_3$), 3.70 (s, 3 H, CH$_3$); mass spectrum *m/e* 198.

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.82; H, 7.32.

Preparation of the Brosylate of Dimethyl *trans*-4-Hydroxycyclohexane-*cis*-1,2-dicarboxylate.—To a solution of 1.80 g (9.0 mmol) of dimethyl *trans*-4-hydroxycyclohexane-*cis*-1,2-dicarboxylate[19] in 10 ml of dry pyridine was added 3.0 g (11.7 mmol) of brosyl chloride. The mixture was allowed to stand overnight in the refrigerator. The solution was filtered from the pyridine hydrochloride and poured into water. The aqueous mixture was extracted with ether. The ether solution was washed with dilute hydrochloric acid, followed by a saturated solution of sodium bicarbonate. The ether solution was dried (K_2CO_3, Na_2SO_4) and the ether removed by rotary evaporation. The residue (1.85 g) was dissolved in an ether–pentane mixture. The solution was cooled; the brosylate, which first oiled out, crystallized on standing several days in the freezer. The crystalline cake was crushed under pentane. The solid was washed with more pentane and dried at reduced pressure. The resulting brosylate showed mp 58–64°; nmr $\delta_{TMS}^{CDCl_3}$ 1.50–2.23 (m, 6 H, methylenes), 2.76–3.11 (m, 2 H, CHCOOCH$_3$), 3.73 (s, 6 H, CH$_3$), 4.63–4.98 (m, 1 H, CHOBs), 7.71 (s, 4 H, aromatic).

Anal. Calcd for $C_{16}H_{19}BrO_7S$: C, 45.83; H, 4.57. Found: C, 45.54; H, 4.32.

The Reaction of the Brosylate of Dimethyl *trans*-4-Hydroxycyclohexane-*cis*-1,2-dicarboxylate with Potassium *tert*-Butoxide.—A solution of potassium *tert*-butoxide in 20 ml of *tert*-butyl alcohol was prepared by refluxing 0.251 g (6.425 mmol) of potassium in the alcohol. This solution was added dropwise with stirring to a solution of 2.8 g (6.425 mmol) of **18** in 10 ml of *tert*-butyl alcohol over a 20-min period. The mixture was stirred for an additional 15 min. Solid ammonium chloride (1.0 g) was added. The *tert*-butyl alcohol was removed by rotary evaporation. The residue was diluted with water and extracted with ether. The ether solution was dried ($MgSO_4$) and the ether was removed by rotary evaporation. The residue (1.10 g) was distilled [bath temperature 110° (0.1 mm)] to give a 3:2 mixture (0.88 g, 67%) of **dimethyl bicyclo[3.1.0]hexane-1,*exo*-2-dicarboxylate (19)** and **17** as determined by nmr analysis.

Equilibration of 17 and 19.—A solution of 0.150 g (0.757 mmol) of **17** in 2 ml of methanol containing a small amount of sodium methoxide was refluxed for 24 hr. The mixture was

diluted with ether, treated with Norit, and filtered. The ether was removed by rotary evaporation. Nmr analysis of the residue showed the presence of the endo and exo isomers in a 78:22 ratio.

When an isomer mixture containing 60% exo isomer and 40% endo isomer was subject to the above reaction conditions, the endo–exo ratio was found to be 76:24.

Hydrobromination of 4.—Hydrogen bromide was bubbled into a solution of 0.50 g (2.55 mmol) of **4** in 8 ml of chloroform for 45 sec. The mixture was allowed to stand at room temperature for 30 min. The solvent was removed at reduced pressure, leaving 0.69 g (100%) of a mixture of **20** and **21**. The mixture was taken up in boiling hexane. The solution was allowed to stand for several hours at room temperature. Filtration gave 0.250 g of pure dimethyl *exo*-**4-bromobicyclo[3.1.0]hexane-1,*exo*-2-dicarboxylate** (**20**): mp 103–105°; ν_{max}^{KBr} 2985, 2935, 2912, 2810, 1741, 1720 cm^{-1}; nmr $\delta_{TMS}^{CDCl_3}$ 0.70–1.35 (AB of an ABX, 2 H, cyclopropyl methylene, $J_{AB} = -5.7$ Hz), 2.23–2.47 (m, 2 H, cyclopentyl methylene), 2.52–2.77 (X of an ABX, 1 H, cyclopropyl methine, $J_{AX} + J_{BX} = 13.5$ Hz), 3.20 (t, 1 H, CHCOOCH$_3$), 4.32 (t, 1 H, CHBr), 3.68 (s, 3 H, CH$_3$), 3.72 (s, 3 H, CH$_3$).

Anal. Calcd for $C_{10}H_{13}O_4Br$: C, 43.34; H, 4.73; Br, 28.84. Found: C, 43.53; H, 4.75; Br, 28.72.

The hexane was removed from the filtrate by rotary evaporation, leaving 0.403 g of a liquid which was subjected to molecular distillation, giving **dimethyl *exo*-4-bromobicyclo[3.1.0]hexane-1,*endo*-2-dicarboxylate** (**21**) contaminated with only a trace of **20**: ν_{max}^{neat} 2970, 2930, 2830, 1735 cm^{-1}; nmr $\delta_{TMS}^{CDCl_3}$ 1.13–1.68 (AB of an ABX, 2 H, cyclopropyl methylene, $J_{AB} = -5.9$ Hz), 1.95–2.63 (m, 3 H, cyclopropyl methine, cyclopentyl methylene), 3.83 (m, 1 H, CHCOOCH$_3$), 3.67 (s, 6 H, CH$_3$), 4.49 (d, 1 H, CHBr, $J = 4.8$ Hz).

Anal. Calcd for $C_{10}H_{13}O_4Br$: C, 43.34; H, 4.73, Br, 28.84. Found: C, 43.60; H, 4.85; Br, 28.53.

The ratio of **20** to **21** was found to be 44:56 by integration of the methyl resonances in the nmr spectrum of the mixture; the methyl resonances were resolved by the addition of Eu(fod)$_3$-d_{30}. Samples of both isomers, when subjected to the reaction conditions, were recovered unchanged.

The above reaction was repeated, using deuterium bromide. Nmr analysis of the separated isomers indicated that in each case only the hydrogen α to the carbomethoxy group was replaced by deuterium.

The Reaction of Dimethyl *trans*-4,5-Dibromocyclohexane-*cis*-1,2-dicarboxylate (**22**) **with Sodium Hydride.**—A solution of 12.0 g (0.0355 mol) of **dimethyl *trans*-4,5-dibromocyclohexane-*cis*-1,2-dicarboxylate** (**22**) in 400 ml of dry THF containing 1.85 g (0.077 mol) of sodium hydride was refluxed with stirring for 48 hr. The mixture was filtered and the THF removed by rotary evaporation. The residue was mixed with an aqueous solution of ammonium chloride and extracted with ether. The ether solution was dried (MgSO$_4$) and the solvent was removed by rotary evaporation. The residue was distilled [95–100° (0.05 mm)], giving 6.0 g (65%) of **21**. This material is identical with the major isomer isolated from the hydrobromination of **4** as determined by nmr and ir spectra, as well as vpc retention times.

Hydrogenolysis of 21.—A solution of 0.25 g (0.91 mmol) of **21**, 0.5 g of sodium acetate, and 0.10 g of Pd/C (5%) in 3 ml of acetic acid was hydrogenated at atmospheric pressure for 23 hr. The mixture was filtered and poured into water. The aqueous mixture was extracted with ether. The ether solution was washed with a saturated solution of sodium bicarbonate and dried (MgSO$_4$). The ether was removed by rotary evaporation, leaving 0.180 g (100%) of **17**, determined from its nmr spectrum and vpc retention time.

Hydrogenolysis of 20.—A 0.080-g (0.289 mmol) sample of **20** was hydrogenated for a total of 48 hr using the above procedure, giving 0.053 g (93%) of **19**. An analytical sample was isolated *via* preparative vpc (6 ft × 0.25 in. glass column, Carbowax 20M on 60–80 mesh Chromosorb Q, 160°): $\nu_{max}^{CCl_4}$ 2915, 2845, 2813, 1731 cm^{-1}; nmr $\delta_{TMS}^{CDCl_3}$ 3.60 (s, 3 H, CH$_3$), 3.66 (s, 3 H, CH$_3$), 2.95–3.17 (m, 1 H, CHCOOCH$_3$), 0.75–2.30 (m, 7 H, saturated).

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.72; H, 7.17.

The Interconversion of 20 and 21.—A solution of 0.100 g (0.37 mmol) of **20** and 0.014 g of sodium hydride in 2 ml of THF was stirred at reflux for 2 hr and at room temperature for 16 hr. A few drops of acetic acid were added, and the mixture was poured into a saturated solution of ammonium chloride. The mixture was extracted with ether. The ether solution was washed with a saturated solution of sodium bicarbonate and dried (MgSO$_4$). The ether was removed at reduced pressure, giving 0.065 g of a liquid. Nmr and vpc analysis (Carbowax 20M on 60–80 mesh Chromosorb W, 165°) of the liquid indicated it was composed of **21**, dimethyl phthalate, and an unidentified component; the ratio of the respective areas of the vpc trace was 69:13:18.

Equilibration of Dimethyl *exo*- and *endo*-4-Bromobicyclo[3.1.0]-hexane-1,*endo*-2-dicarboxylates (**21 and 23**).—To a solution of 0.150 g (0.54 mmol) of **21** in 1 ml of DMF was added 0.30 g (3.5 mmol) of lithium bromide. The solution was stirred at room temperature for 30 min, poured into water, and extracted with ether. The ether solution was washed with water and dried (MgSO$_4$). The ether was removed at reduced pressure, giving 0.110 g (73%) of a mixture of **21** and **23**; the ratio of the two isomers was found to be 56:44 by integration of the methyl resonances in the nmr spectrum of the crude reaction mixture; the methyl resonances were resolved by the addition of Eu(fod)$_3$-d_{30}.

These isomers were shown to differ only in the configuration at the carbon atom bearing the bromine by hydrogenolysis of the mixture (5% Pd/C, NaOAc, HOAc, 48 hr) to give **17**.

A similar mixture of isomers was obtained by passing **21** through a column packed with UCON nonpolar on 60–80 mesh Chromosorb W at 190°.

Equilibration of Dimethyl *exo*-and *endo*-4-Bromobicyclo[3.1.0]-hexane-1,*exo*-2-dicarboxylates (**20 and 24**).—To a solution of 0.080 g (0.289 mmol) of **20** in 0.75 ml of DMF was added 0.20 g (2.3 mmol) of lithium bromide. The mixture was maintained at 100° for 1 hr and then poured into water. The aqueous mixture was extracted with ether. The ether solution was washed with water and dried (MgSO$_4$). The ether was removed at reduced pressure, giving 0.074 g (92%) of a mixture of **20** and **24** in a ratio of 20:80, respectively; the ratio was determined from integration of the methyl resonances in the nmr spectrum of the crude reaction mixture; these resonances were resolved by the addition of Eu(fod)$_3$-d_{30}.

These isomers were shown to differ only in the configuration at the carbon atom bearing the bromine by hydrogenolysis of the mixture (5% Pd/C, NaOAc, HOAc, 72 hr) to give **19** as the major product.

Registry No.—**2**, 38665-90-6; **3**, 38665-91-7; **4**, 38665-92-8; **7**, 14309-54-7; **8**, 38665-94-0; **9**, 38665-95-1; **10**, 38665-96-2; **17**, 38665-97-3; **19**, 38665-98-4; **20**, 38665-99-5; **21**, 38666-00-1; maleic anhydride, 108-31-6; *trans*-1,4-dichloro-2-butene, 110-57-6; dimethyl *trans*-4-hydroxycyclohexane-*cis*-1,2-dicarboxylate, 7731-16-0; dimethyl *trans*-4-hydroxycyclohexane-*cis*-1,2-dicarboxylate brosylate, 38666-01-2.

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The Formation and the Mass Spectra of Adducts from the Reaction of Some α-Substituted Vinylcyclopropanes with Benzyne[1]

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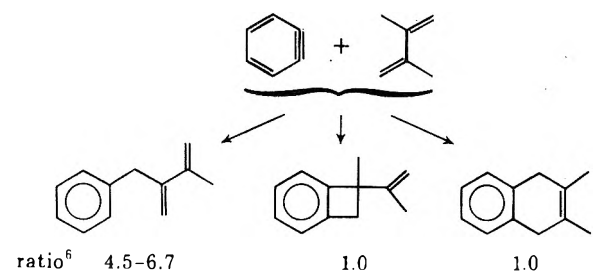
The reactions of benzyne, generated by the thermolysis of benzenediazonium-2-carboxylate, with 1,1-dicyclopropylethylene (1), 2-cyclopropylpropene (6), and α-cyclopropylstyrene (11) are herein described. Benzyne shows no tendency to add across the vinylcyclopropane systems in 1, 6, and 11. With substrates containing proper allylic hydrogens, the "ene" reaction (6 → 7 → 10) exceeds that of [2 + 2] cycloaddition (6 → 9). When the allylic hydrogens are part of a cyclopropane ring, the [2 + 2] cycloaddition (1 → 2) or the Diels–Alder reaction (11 → 13 → 14) prevail. In the case of 1, the 1 → 2 conversion was accompanied by a novel "ene" reaction involving the cyclopropane methine hydrogen (1 → 3). The intermediacy of a diradical species of structure 17 was invoked to explain the 1 → 2 and 1 → 3 conversions. Small amounts of 3-cyclopropyl-3-phenylisochroman-1-one (12) were isolated from the reaction of 11 with benzyne. Peaks corresponding to ions M − CH_3 and M − C_2H_5, and/or M − C_2H_4, M − C_3H_5, M − C_3H_7, and M − C_4H_3, are prominent in the mass spectra of most of the adducts described herein. The appearance of M − CH_3 and M − C_2H_5 ions implies rearrangement of the cyclopropyl group followed by hydrogen migration prior to fragmentation. Ionized 3 and 10 are featured by the loss of either cyclopropyl or benzyl radical to yield the methylenecyclopropane (21 and 30) and phenylvinylcyclopropane (33) cations, respectively.

The olefinic character of cyclopropane is manifested by (1) its tendency to undergo addition reactions and (2) its ability to enter into conjugation with adjacent double bonds.[2] Thus, vinylcyclopropanes are analogous to some degree to conjugated dienes. For example, properly activated vinylcyclopropanes lend themselves to thermal [2 + 5] cycloaddition[3] where a cyclopropane bond provides a source of two electrons.[4]

To explore further the scope of the reaction, which can be labeled as a [$_\sigma$2 + $_\pi$2 + $_\pi$2] cycloaddition, a study of the reaction of benzyne with some α-substituted cyclopropylethylenes was undertaken. Benzyne is known to react with dienes containing readily accessible allylic hydrogens, preferably by the "ene" synthesis analogous to the Diels–Alder reaction,[5] or, in absence of such hydrogens, by [2 + 2] and/or [2 + 4] cycloaddition (Schemes I, II, and III).[6-8]

On the McEwen–Streitwieser–Applequist–Dessy pK_a scale[9] the cyclopropane hydrogens are 3.5 pK_a units less acidic than the allylic hydrogen in propylene. Furthermore, from Shatenstein's hydrogen–deuterium exchange experiments[10] it is known that the ring methine hydrogen in alkylcyclopropane is less acidic than the ring methylene hydrogens, which, in turn, are comparable in acidity to aromatic hydrogens in alkylbenzenes. Vinylcyclopropane, therefore, is not ex-

SCHEME I



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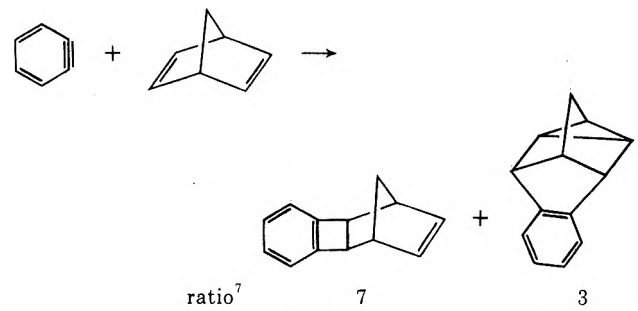

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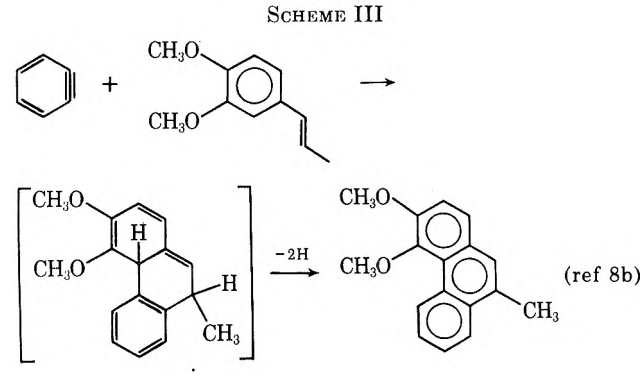


(1) Presented before the 41st National Meeting of the Israel Chemical Society, Tel Aviv, Oct 1971; V. Usieli, L. Friedman, and S. Sarel, Abstract of Papers, p 201.

(2) (a) M. Smith in Rodd's "Chemistry of Carbon Compounds," Vol. II, 2nd ed, S. Coffey, Ed., Elsevier, Amsterdam, 1967, Part A, pp 19–70; (b) R. Breslow in "Molecular Rearrangements," Vol. 1, P. de Mayo, Ed., Interscience, New York, N. Y., 1963, p 233; (c) N. C. Deno, *Progr. Phys. Org. Chem.*, **2**, 129 (1964); (d) S. Sarel, J. Yovell, and M. Sarel-Imber, *Angew. Chem., Int. Ed. Engl.*, **7**, 577 (1968); (e) S. Sarel and R. Ben-Shoshan, *Tetrahedron Lett.*, 1053 (1965); (f) J. A. Landgrebe and J. D. Shoemaker, *J. Amer. Chem. Soc.*, **89**, 4465 (1967); (g) A. Maercker, *Justus Liebigs Ann. Chem.*, **732**, 151 (1970).

(3) For possible [$_\sigma$2 + $_\pi$2 + $_\pi$2] cycloaddition see (a) S. Sarel and E. Breuer, *J. Amer. Chem. Soc.*, **81**, 6522 (1959); (b) F. W. Fowler, *Angew. Chem., Int. Ed. Engl.*, **10**, 135 (1971); (c) J. E. Baldwin and R. K. Pinschmidt, Jr., *Tetrahedron Lett.*, 935 (1971); (d) R. Noyori, N. Hayashi, and M. Kato, *J. Amer. Chem. Soc.*, **93**, 4948 (1971).

(4) For possible [$_\sigma$2$_a$ + $_\sigma$2$_a$ + $_\pi$2$_a$] cycloadditions, see C. D. Smith, *ibid.*, **88**, 4273 (1966).

(5) (a) For a review of "ene" reaction, see H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 556 (1969); (b) R. W. Hoffmann, "Dehydrobenzene and Cycloalkynes," Academic Press, London, 1967, p 197.

(6) G. Wittig and H. Dürr, *Justus Liebigs Ann. Chem.*, **672**, 55 (1964).

(7) H. E. Simmons, *J. Amer. Chem. Soc.*, **83**, 1657 (1961); also ref 5b, p 235.

(8) (a) M. Stiles, U. Burkhardt, and A. Haag, *J. Org. Chem.*, **27**, 4715 (1962); (b) S. F. Dyke, A. R. Marshall, and J. P. Watson, *Tetrahedron*, **22**, 2515 (1966).

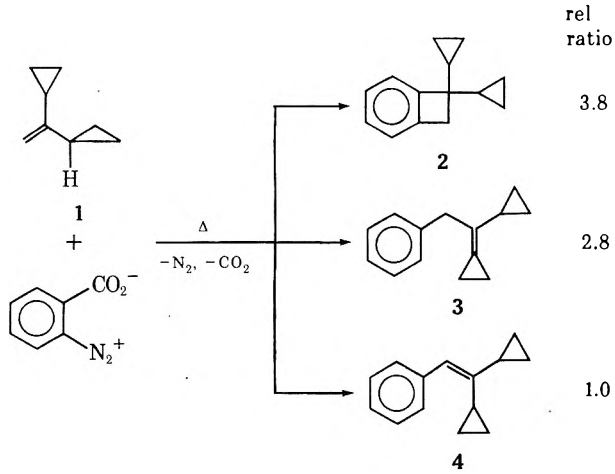
(9) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 19.

(10) A. I. Shatenstein, *Advan. Phys. Org. Chem.*, **1**, 176 (1963); ref 9, pp 22–23.

pected to react with benzyne by the "ene" synthesis but rather to give rise to cycloaddition products.

We found that on exposure of 1,1-dicyclopropylethylene (**1**) to the action of benzyne generated by the thermolysis of benzenediazonium-2-carboxylate in $(CH_2Cl)_2$ a mixture of three isomeric adducts is obtained (30% yield), in the ratio of 3.8:2.8:1 (Scheme IV).

SCHEME IV



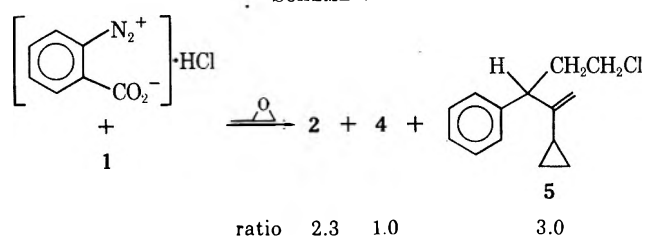
The major component was shown to be a four-membered cycloadduct, identified as 3,3-dicyclopropylbenzocyclobutene (**2**) in the following way. It was analyzed as a $C_{14}H_{16}$ compound. Its nmr and ir spectra indicated the presence of a 1,2-disubstituted benzene ring, and two cyclopropyl groups, with observed resonance up to τ 10.36, and two methylene protons of a cyclobutene ring appearing as a singlet at τ 7.15.

The two other products proved to be isomeric compounds where the more abundant one most likely results from the "ene" synthesis, involving one of the cyclopropane methine hydrogens, and was assigned the α-cyclopropylphenethylidenecyclopropane structure (**3**). Its structure was inferred from the mass spectrum, showing the parent peak at *m/e* 184, and from its nmr spectrum, indicating the presence of one benzyl, one cyclopropyl, and one cyclopropylidene group in the molecule.

The minor product was assigned similarly the 1,1-dicyclopropyl-2-phenylethylene (**4**) structure. Its uv spectrum is characterized by two well-defined peaks of similar intensity at 255 and 205 mμ, attributable to the styrene and the vinylcyclopropane chromophores, respectively. The origin of **4** is not known. It could well be an artifact of **3** as a result of a 1,3-hydrogen shift to yield the thermodynamically more favored conjugated system **4**.

In another experiment, **1** was allowed to react with benzyne which was generated by a slightly different method (method B, Experimental Section), from benzenediazonium-2-carboxylate hydrochloride and propylene oxide. This led to higher yields of reaction products **2** and **4** and a new adduct (major product) which analyzed as a $C_{14}H_{17}Cl$ compound (see Scheme V). Its mass spectrum was characterized by two peaks at *m/e* 220 and 222, corresponding to the molecular ions, in the ratio expected for the presence of the

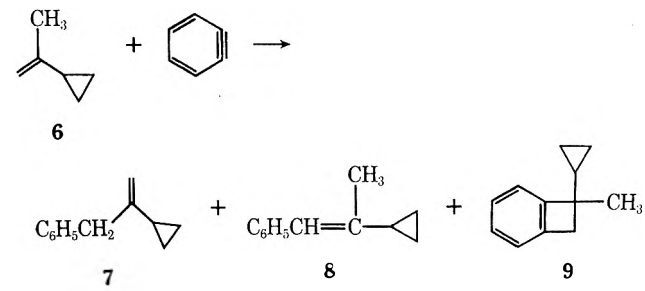
SCHEME V



^{35}Cl and ^{37}Cl isotopes of chlorine. It was assigned the 4-cyclopropyl-3-phenylpent-4-enyl chloride structure (**5**) on the basis of its spectroscopic properties (see Experimental Section).

The reaction of benzyne with a threefold excess of 2-cyclopropylpropene (**6**) has been shown[11] to give a 38% yield of three adducts, **7**–**9**, in the ratio of 19.5:4.5:1 (Scheme VI).

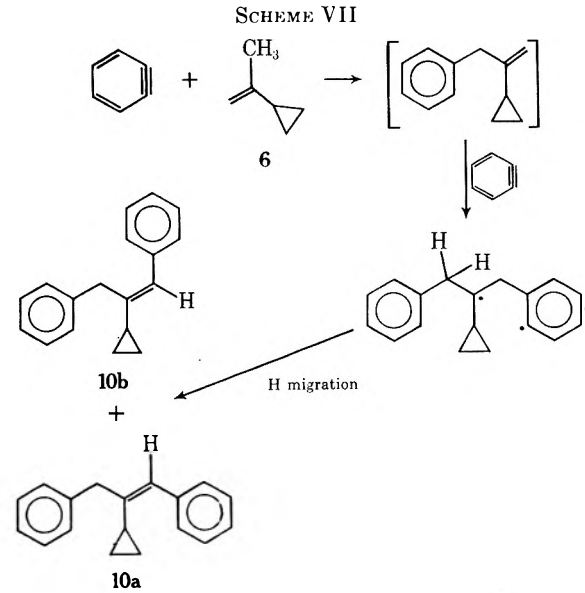
SCHEME VI



When 2 mol of benzyne were allowed to react with 1 mol of **6** (instead of the 1:3 ratio employed by the Japanese authors[11]), a 55% yield of a mixture of two products in the ratio of 5:1 was obtained.

The two products were shown to be geometric isomers of 2-cyclopropyl-1,3-diphenylpropene (**10a** and **10b**, see Scheme VII). The isomeric mixture analyzed

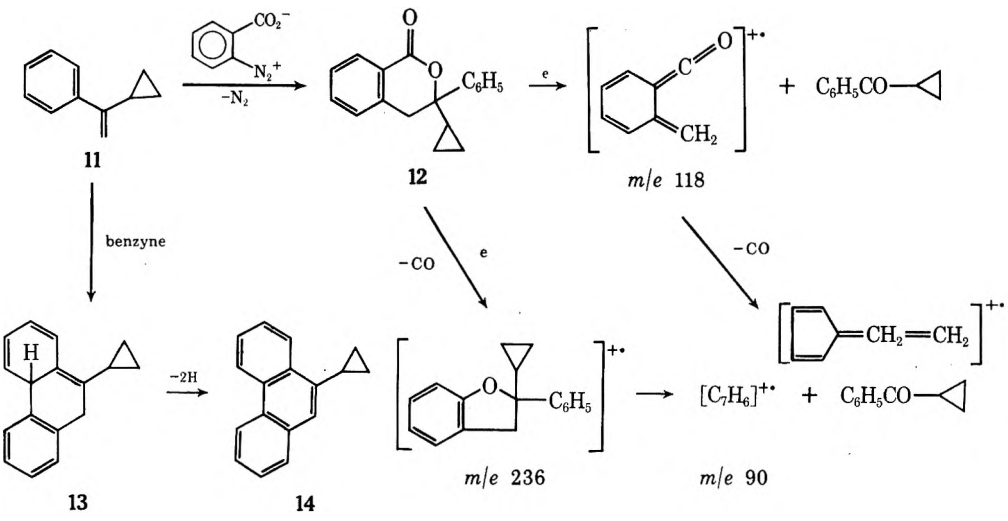
SCHEME VII



as $C_{18}H_{18}$ compounds, exhibiting the parent peak at *m/e* 234 in the mass spectrum. The nmr spectrum shows a ten-proton aromatic multiplet centered at τ 2.9, a singlet at 3.63 for the predominant isomer, and

(11) I. Tabushi, K. Okazaki, and R. Oda, *Tetrahedron*, **25**, 4401 (1969).

SCHEME VIII



another singlet at 3.78 for the minor product (the integrated area for the two corresponds to one proton), a singlet at 6.44 for the major product, and another singlet at 6.75 for the minor product (the integrated area of which corresponds to two protons).

It has been shown[2d] that in vinylcyclopropane systems of the a and b types (see Scheme VII) the vinylic proton cis to the cyclopropane resonates at a higher field than the corresponding proton in the trans arrangement. The difference of 0.15 ppm between the vinylic protons permits us to assign the trans geometry (**10a**) to the predominant isomer, and the cis geometry (**10b**) to the minor product.

The uv spectrum of **10a** + **10b** displays two intense bands at 250 and 209 mμ, assignable to the styrene and the vinylcyclopropane chromophores, respectively. The extinction coefficient at the lower wavelength markedly exceeds that at the longer wavelength of the spectrum.

The reaction of α-cyclopropylstryene (**11**) with benzyne (Scheme VIII) resulted in a 10% yield of two compounds in the ratio of 1:8.5. The major product was identified as 9-cyclopropylphenanthrene (**14**) on the basis of its analysis and spectroscopic properties. In its mass spectrum the molecular ion at *m/e* 218 is the base peak, reflecting the remarkable stability of the aromatic polycyclic nucleus. Other peaks with abundances >25% of the base peak are at *m/e* 217 (M − 1, 61%), at *m/e* 203 ($C_{16}H_{11}$, 72%), corresponding to the loss of methyl from the parent ion (as evidenced by the presence of a metastable peak at *m/e* 189), and at *m/e* 202 ($C_{16}H_{10}$, 54%) arising from further fragmentation of the ion of *m/e* 217 by loss of methyl, as substantiated by the presence of a metastable ion (m* 188) in the spectrum. Study has shown that the ion of *m/e* 217 lends itself to two more reactions: (i) the loss of acetylene to give the ion of *m/e* 191 ($C_{15}H_{11}$, 40%); (ii) the loss of ethylene to yield the ion of *m/e* 189 ($C_{15}H_9$, 21%). Its uv spectrum shows the typical phenanthrene absorption bands at 252 and 221 mμ[12] with high extinction coefficients (see Figure 1). The nmr data (see Experimental Section) are in agreement with structure **14**.

The minor product from the reaction of **11** with benzyne was assigned the structure of 3-cyclopropyl-3-phenylisochroman-1-one **12** on the basis of its ir spectrum, exhibiting the lactone carbonyl absorption at 1720 cm^{-1}, and its molecular ion at *m/e* 264 ($C_{18}H_{16}O_2$) in the mass spectrum. The base peak of the spectrum is at *m/e* 118 (C_8H_6O) corresponding to the loss of cyclopropyl phenyl ketone.[13] Other peaks with abundances >40% of the base peak are at *m/e* 236 ($C_{17}H_{16}O$, 50%), corresponding to the loss of carbon monoxide from the parent ion, and *m/e* 90 (C_7H_6, 40%), arising either from further fragmentation of the ion of *m/e* 118 by loss of carbon monoxide or from the ion of *m/e* 236 by loss of cyclopropyl phenyl ketone. The nmr spectrum shows a one-proton aromatic multiplet centered at τ 2.03 and an eight-proton aromatic multiplet between 2.35 and 2.95. In addition, the benzylic protons appear as a singlet at τ 6.43.

The data produced above clearly reflect the tendency of α-cyclopropylstyrene to behave toward

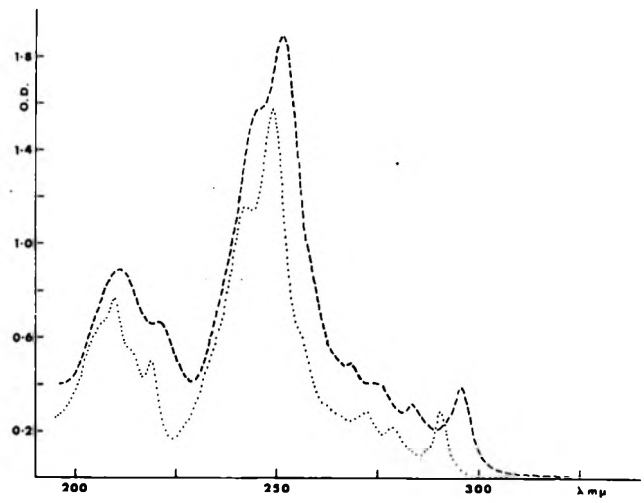


Figure 1—Ultraviolet absorption spectra of 3.10×10^{-5} mol/l. 9-cyclopropylphenanthrene (**14**) (----) and of 2.16×10^{-5} mol/l. phenanthrene (····) in *n*-hexane.

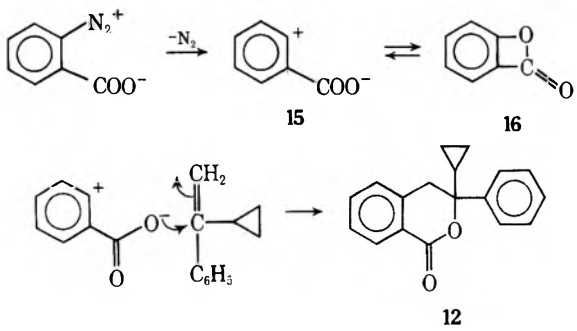
(12) N. O. V. Sonntag, S. Linder, E. I. Becker, and P. E. Spoerri, *J. Amer. Chem. Soc.*, **75**, 2283 (1953).

(13) Compare with similar electron impact induced elimination of acetaldehyde from derivatives of 3-methylisochroman-1-one: (a) M. J. Rix and B. R. Webster, *J. Chem. Soc. B*, 254 (1968); (b) J. F. Grove, *J. Chem. Soc., Perkin Trans. 1*, 2400 (1972); (c) see also D. R. Arnold, E. Hedaya, V. Y. Maritt, L. A. Karnischky, and M. E. Kent, *Tetrahedron Lett.*, 3917 (1972).

benzyne as a true styrene,[14] undergoing a [2 + 4] cycloaddition followed by dehydrogenation (**11** → **13** → **14**). The [2 + 2] cycloaddition and the "ene" reaction, which are displayed by **1**, could not be observed in the case of **11**. Most significantly, benzyne shows no tendency to add across the vinylcyclopropane system, as do the acetylenedicarboxylic acid esters.[3b,c]

The immediate precursor of **12** is most likely the zwitterion **15**, presumably being formed *via* expulsion of a nitrogen molecule from benzenediazonium-2-carboxylate (Scheme IX). The low yield of **12** suggests

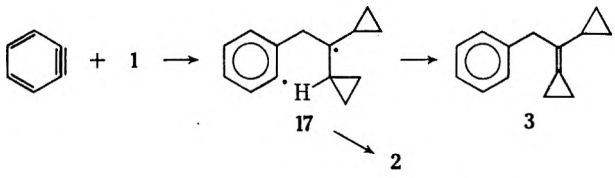
SCHEME IX



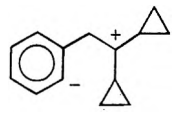
that **15** does not appreciably equilibrate with its cyclic form **16**.[5b]

Mechanism.—The formation of **3** from **1** can be best explained in terms of a multistage process involving a diradical intermediate **17**, which *via* intramolecular 1,5-hydrogen shift gives rise to "ene" synthesis (Scheme X).

SCHEME X



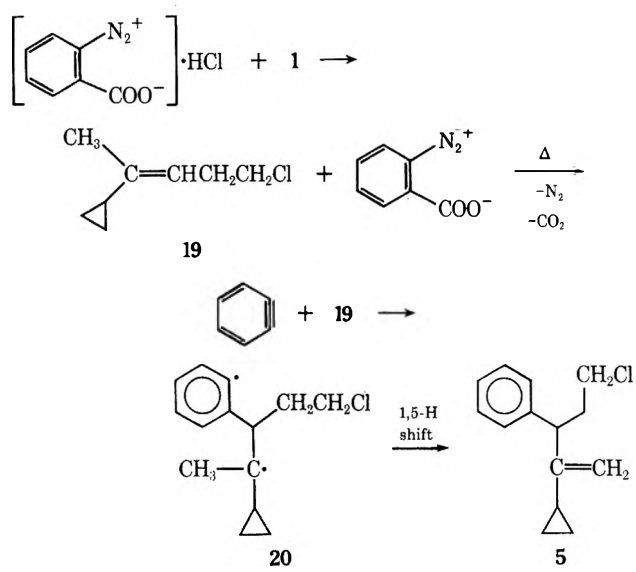
The intermediacy of a dipolar adduct **18** appears less likely, since it implies that in the conversion of **18**



to **3** the more acidic C–H bond (aromatic) is formed *via* migration of a proton from the less acidic C–H bond (the methine cyclopropane C–H bond). Indeed, formation of **3** in this reaction should be viewed as a substantiation for the radical mechanism.[15] The formation of **5** from **1** (Scheme V) most likely occurs *via* HCl-induced homoallylic rearrangement (**1** → **19**) followed by benzyne addition (**19** → **20** → **5**) as delineated in Scheme XI.

Mass Spectra.—The mass spectra were measured on a Varian CH5 mass spectrometer using the direct

SCHEME XI



inlet system. The electron energy was maintained at 70 eV and the ionization current at 20 μA. The abundances of the prominent ions in the mass spectra of compounds **2**, **3**, **4**, and **10** are assembled in Table I and given in percentages relative to the base peaks in the spectra.

TABLE I

RELATIVE ABUNDANCES OF PROMINENT IONS IN THE MASS SPECTRA OF **2**, **3**, **4**, **5**, AND **10**

m/e	**2**	**3**	**4**	**5**	**10**
77	11.0	33.0	47.4	21.6	
91	9.0	100	91.7	84.3	60.4
93		35.0	30.0		
115	69.6	28.0	72.4	56.0	35.2
128	63.8	46.1	100		52.1
129	21.7	32.8	49.4	100	14.1
141	100	47.2	99.4		13.8
142	20.6	29.4	39.1		9.4
143	14.2	27.2	80.0	58.2	100
155	37.7	26.7	80.1		
156	46.4	7.8	35.3		
157				56.0	
169	17.7	23.9	70.5		
M·+	3.2	3.9	73.7	46.3	45.0

The principal electron-induced fragmentation of saturated cyclopropanes was shown[16a,b] to involve the rupture of the small ring in two main modes: (a) cleavage of the cyclopropane 1,2 bond to yield ions of a "normal" propane chain which then eject a neutral ethylene derivative, and (b) cleavage of the 2,3 bond to yield a branched ionic biradical propane followed by loss of a neutral C_3 unit with retention of the charge on the substituent (see Scheme XII).

The mass spectra of the [2 + 2] cycloadduct **2** and of the "ene" reaction products, **3** and **4**, from the reaction of **1** with benzyne are characterized by six peaks at *m/e* 169, 155, 143, 141, 128, and 115, corresponding to the ionic fragments M − CH_3, M − C_2H_5, M − C_3H_5, M − C_3H_7, M − C_4H_8, and M − C_5H_9, respectively. The first two ionic species, M − CH_3 and M − C_2H_5, probably originate from an initial 1,2-bond fission of one of the cyclopropyl groups with concomitant

(14) (a) W. Davies and J. R. Wilmshurst, *J. Chem. Soc.*, 4079 (1961); (b) T. G. Corbett and Q. N. Porter, *Aust. J. Chem.*, **18**, 1781 (1965).

(15) (a) M. Jones, Jr., and R. H. Levin, *J. Amer. Chem. Soc.*, **91**, 6411 (1969); (b) P. G. Gassman and H. P. Benecke, *Tetrahedron Lett.*, 1089 (1969).

(16) (a) H. Weitkamp, U. Hasserodt, and F. Korte, *Chem. Ber.*, **95**, 2280 (1962); (b) N. Turro, *et al.*, *J. Amer. Chem. Soc.*, **87**, 4097 (1965).

double hydrogen migrations to yield *n*-propyl radical ions which then eject a methyl and/or an ethyl radical.

From Table I it can be seen that the relative intensity of the molecular ion peak in the mass spectra of **2**, **3**, **4**, and **10** decreases in the order **4** > **10** > **3** ≈ **2**, suggesting that the cation radicals produced by loss of an electron from either **4** or **10** are more stable than those derived from **2** or **3**. This is in harmony with the observed unusually low ionization potentials in cyclopropylethylenes[17] probably due to the ability of the small ring to stabilize an adjacent electron-deficient center.[18]

Of particular interest are the two primary mass spectral reactions of geminal benzylcyclopropylmethylenecyclopropane (**3**), featured by the loss of either cyclopropyl radical or benzyl radical to give the respective methylenecyclopropane cations **30** and **21**. The latter subsequently loses two atoms of hydrogen to yield a highly stable ionic fragment (*m/e* 91, base peak) to which we assign the cyclobutenylcylclopropenylium ion structure **22**, constituting an isoelectronic species of the well-known tropylium ion (**23**). A metastable peak observed at *m/e* 46.6 could result from the **3** → **21** route (calculated metastable 47.0) or from the elimination of an acetylene molecule from the tropylium ion (**23**) to form the cyclopentadienylium ion (**24**) of *m/e* 65 (relative abundance 22%; calculated metastable 46.4). Significantly, the abundance of the benzylmethylenecyclopropylium ion (**30**) is considerably less prominent in the spectrum of **3** (see Table I). This suggests that ionized benzylcyclopropylmethylenecyclopropane (**3**) ruptures α to the vinyl bond in two main modes: (i) cleavage of the benzyl–vinyl bond gives the cyclopropylmethylenecyclopropylium ion, which then loses two hydrogen atoms to give the highly stable ion **22**; and (ii) cleavage of the cyclopropyl–vinyl bond with retention of charge on the substituted methylenecyclopropane moiety[19-21] (Scheme XIII).

The importance of the latter mass-spectral pattern is further demonstrated in the case of ionized **10**, in which the dominating primary reaction involves

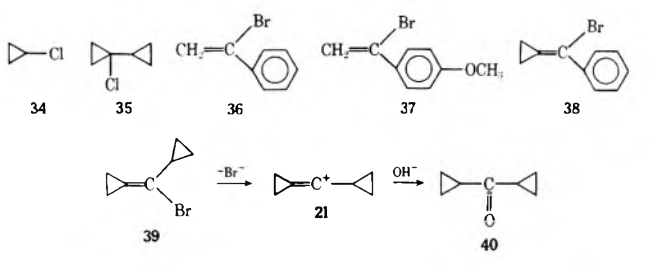
(17) S. Nishida, I. Moritani, and T. Traji, *J. Chem. Soc., Chem. Commun.*, 1114 (1972).

(18) C. D. Poulton and S. Winstein, *J. Amer. Chem. Soc.*, **94**, 2297 (1972).

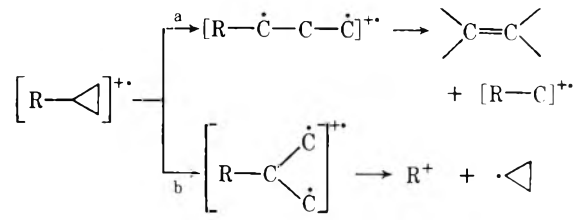
(19) (a) H. G. Richey and J. M. Richey in "Carbonium Ions," Vol. 2, G. A. Olah and P. v. R. Schleyer, Ed., Wiley-Interscience, New York, N. Y., 1970, p 899; (b) M. Hanack, *Accounts Chem. Res.*, **3**, 209 (1970); (c) G. Modena and U. Tonellato, *Advan. Phys. Org. Chem.*, **9**, 185 (1971).

(20) (a) S. A. Sherrod and R. G. Bergman, *J. Amer. Chem. Soc.*, **93**, 1925 (1971); (b) D. R. Kelsey and R. G. Bergman, *ibid.*, **93**, 1941, 1953 (1971).

(21) (a) J. A. Landgrebe and L. W. Becker, *ibid.*, **90**, 395 (1968), report that cyclopropyl substitution (**34** → **35**) enhances the solvolytic propensity of cyclopropyl chloride (**34**) by a factor of 286,000; (b) M. Hanack, private communication, observed a similar enhancing effect of cyclopropyl substitution in solvolysis of vinyl bromides. Thus, the relative rates increase on going from **36** to **37**, to **38**, to **39** by a factor of 10^3, 10^4, 10^6, respectively. The intermediacy of **21** is invoked to explain the facile conversion of **39** to **40**.



SCHEME XII



fission of the benzyl–vinyl bond to give a phenylvinylcyclopropane cation (**10** → **33**) and neutral benzyl fragment. The ion **33** then either ejects an ethylene molecule to give the indenylium ion (**29**), or first rearranges into a protonated methylnaphthalene species (**31**) and then loses a methyl radical to give ionized naphthalene (**32**) (Scheme XIV).

Experimental Section

Nmr spectra were recorded on JEOL C-60H spectrometer (internal TMS), uv spectra on a Unicam SP 800 A spectrophotometer, ir spectra on a Perkin-Elmer 237 spectrophotometer, and mass spectra on a MAT CH 5 spectrometer.

Cyclopropylethylenes.—Literature procedures were used for the preparation of 1,1-dicyclopropylethylene (**1**), bp 45° (20 mm), n^{20}D 1.4653,[22a,b] 2-cyclopropylpropene (**6**), bp 70° (690 mm), n^{20}D 1.4250,[23] and α-cyclopropylstyrene (**11**), bp 102–104° (20 mm), n^{25}D 1.5467.[22b,24]

General Procedure for the Reaction of Cyclopropylethylenes with Benzyne. Method A.—Benzenediazonium-2-carboxylate (25 mmol), prepared by the method of Logullo, Seitz, and Friedman,[25] was added to a solution of the olefin in ethylene dichloride. The stirred reaction mixture was refluxed for 1 hr or until gas evolution ceased. The dark solution was then concentrated and chromatographed on neutral alumina (40 g) with ethylene dichloride, carbon tetrachloride, or benzene as eluent. The first fractions contained a mixture of the reaction products and unreacted starting olefin. Separation of the reaction products was carried out by preparative vpc or by preparative tlc.

Method B.—The procedure in method A was followed, but instead of benzenediazonium-2-carboxylate the hydrochloride of this reagent was used, and propylene oxide (2 equiv) was added to the reaction mixture.

Reaction of 1,1-Dicyclopropylethylene (1) with Benzyne (1:1). Method A.—The reaction mixture was chromatographed with ethylene dichloride as eluent. A mixture of three isomeric compounds, **2**, **3**, and **4**, was obtained in a yield of 15, 11, and 4%, respectively. The compounds were separated by preparative vpc (6 ft × 0.25 in. 10% SE-30, at 140°, gas flow rate 57 ml/min).

Compound 2 was a liquid: retention time 13.5 min; nmr (CCl_4) τ 2.65–3.40 (m, 4 H), 7.15 (s, 2 H), 8.53–9.08 (m, 2 H), 9.25–10.36 (m, 8 H); ir 3085–2920, 1470, 1430, 1050, 1020, 755, 725 cm^{-1}; mass spectrum M^+ *m/e* 184.

Anal. Calcd for $C_{14}H_{16}$: C, 91.30; H, 8.70. Found: C, 91.50; H, 8.59.

Compound 3 was a liquid: retention time 20 min; nmr (CCl_4) τ 2.6–3.2 (m, 5 H), 6.58 (s, 2 H), 8.80 (m, 1 H), 9.07 (m, 4 H), 9.43 and 9.55 (two apparent s, 4 H); ir 3085–2910, 1605, 1500, 1455, 1045, 1025, 990, 755, 705 cm^{-1}; mass spectrum M^+ *m/e* 184.

Anal. Calcd for $C_{14}H_{16}$: C, 91.30; H, 8.70. Found: C, 91.40; H, 8.45.

Compound 4 was a liquid: retention time 26 min; nmr (CCl_4) τ 2.6–3.1 (m, 5 H), 3.90 (s, 1 H), 8.13 (m, 1 H), 8.85 (m, 1 H), 9.0–9.65 (m, 8 H); ir 3080–3000, 1630, 1600, 1490,

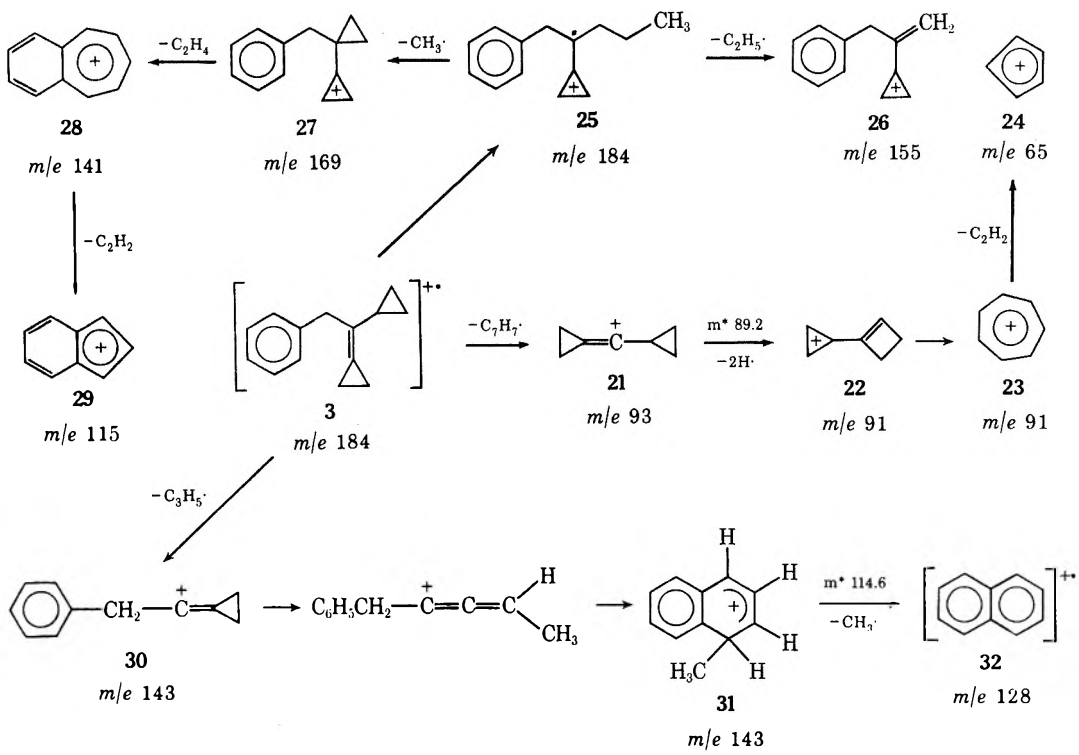
(22) (a) I. A. D'yakonov and I. M. Stroiman, *Zh. Obshch. Khim.*, **33**, 4019 (1963); *Chem. Abstr.*, **60**, 9159g (1964). (b) S. Sarel, R. Ben-Shoshan, and B. Kirson, *Israel J. Chem.*, **10**, 787 (1972).

(23) R. Van Volkenburgh, K. W. Greenlee, J. M. Derfer, and C. E. Boored, *J. Amer. Chem. Soc.*, **71**, 172 (1949).

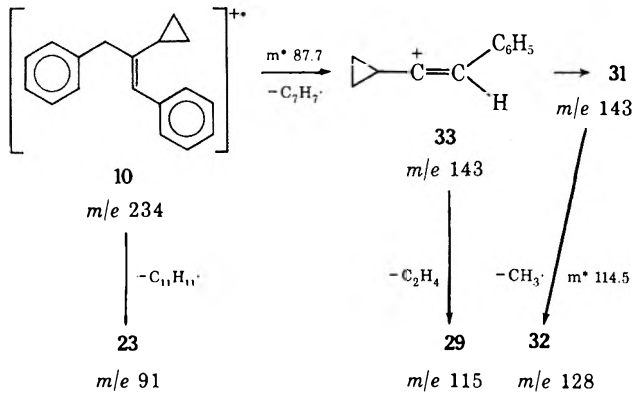
(24) S. Sarel, E. Breuer, Sh. Ertag, and R. Salomon, *Israel J. Chem.*, **1**, 451 (1963).

(25) F. M. Logullo, A. H. Seitz, and L. Friedman, *Org. Syn.*, **48**, 12 (1968).

SCHEME XIII



SCHEME XIV



1445, 1020, 930, 915, 755, 700 cm^{-1}; uv (*n*-hexane) λ_{max} 255 mμ (ε 1.3 × 10^4), 205 (1.4 × 10^4); mass spectrum M$^+$ *m/e* 184.

Anal. Calcd for $C_{14}H_{16}$: C, 91.30; H, 8.70. Found: C, 91.10; H, 8.56.

Reaction of 1,1-Dicyclopropylethylene (1) with Benzyne (1:1). Method B.—The reaction mixture was chromatographed with ethylene dichloride as eluent. A mixture of **2**, **4**, and **5** was obtained in a yield of 17, 7.2, and 21%, respectively. The compounds were separated by preparative vpc, as described above for the reaction of **1** with benzyne, method A.

Compound 5 was a liquid: retention time 40 min; nmr (CCl_4) τ 2.50–2.95 (m, 5 H), 5.25 and 5.33 (2 apparent s, 2 H), 6.31 (t, *J* = 7.5 cps, 1 H), 6.65 (t, *J* = 6 cps, 2 H), 7.73 (m, 2 H), 8.60–9.75 (m, 5 H); ir 3095–2880, 1645, 1605, 1500, 1460, 895, 755, 710 cm^{-1}; mass spectrum M$^+$ *m/e* 220 and 222.

Anal. Calcd for $C_{14}H_{17}Cl$: C, 76.0; H, 7.70; Cl, 16.30. Found: C, 76.08; H, 7.84; Cl, 16.16.

Reaction of 2-Cyclopropylpropene (6) with Benzyne (1:2). Method A.—The reaction mixture was chromatographed with carbon tetrachloride as eluent and one major product, **10**, which consisted of two geometrical isomers, **10a** and **10b** (5:1), was obtained in a yield of 55%. Purification of **10** was effected by preparative vpc without separation of isomers (6 ft × 0.25 in. 10% SE-30, at 205°, gas flow rate 43.5 ml/min).

Isomeric mixture 10 was a liquid: retention time 13.5 min; nmr (CCl_4) τ 2.6–3.1 (m, 10 H), 3.63 (major isomer, **10a**) and 3.78 (minor isomer, **10b**) (two s, 5:1 respectively, 1 H), 6.44 (**10a**) and 6.75 (**10b**) (two s, 5:1 respectively, 2 H), 8.5–9.0 (m, 1 H), 9.3–9.7 (m, 4 H); ir 3080–2900, 1640, 1600, 1495, 1455, 1070, 1045, 1030, 1015, 915, 765, 750, 730, 700 cm^{-1}; uv (*n*-hexane) λ_{max} 250 mμ (ε 1.6 × 10^4), 209 (2.0 × 10^4); mass spectrum M$^+$ *m/e* 234.

Anal. Calcd for $C_{18}H_{18}$: C, 92.31; H, 7.69. Found: C, 92.56; H, 7.70.

Reaction of α-Cyclopropylstyrene (11) with Benzyne (1:1).—The procedure followed was that given in method A with the following variations: (1) chloranil (6.15 g, 25 mmol) was added to the reaction mixture; (2) basic instead of neutral alumina was used for chromatography. The reaction mixture was chromatographed with benzene as eluent. Two products, **14** and **12**, were obtained in a yield of 8.5 and 1%, respectively.

Compound 14 was isolated by preparative vpc (retention time 10 min on 3 ft × 0.25 in. 20% SE-30, at 205°, gas flow rate 33 ml/min) and purified by recrystallization from hexane: colorless crystals; mp 78°; nmr ($CDCl_3$), τ 1.2–1.7 (m, 3 H), 2.2–2.8 (m, 6 H), 7.4–8.0 (m, 1 H), 8.65–9.3 (m, 4 H); ir 3060–2820, 1615, 1590, 1480, 1440, 1010, 875, 750, 735, 715 cm^{-1}; uv (*n*-hexane) λ_{max} 252 mμ (ε 6 × 10^4), 221 (3 × 10^4); mass spectrum M$^+$ *m/e* 218.

Anal. Calcd for $C_{17}H_{14}$: C, 93.58; H, 6.42. Found: C, 93.77; H, 6.48.

Compound 12 was isolated by preparative tlc on silica gel: R_f 0.18 (benzene as eluent); mp 70–72°; nmr ($CDCl_3$) τ 2.03 (m, 1 H), 2.35–2.95 (m, 8 H), 6.43 (s, 2 H), 8.63 (apparent q, 1 H), 9.41 and 9.51 (two apparent s, 4 H); ir 3080–2850, 1720, 1605, 1490, 1460, 1445, 1285, 1235, 1120, 1080, 1025, 1010, 990, 925, 910, 750, 715, 695 cm^{-1}; mass spectrum M$^+$ *m/e* 264, base peak 118.

Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.81; H, 6.06. Found: C, 81.0; H, 6.05.

Registry No.—**1**, 822-93-5; **2**, 38662-40-7; **3**, 38662-41-8; **4**, 23772-96-5; **5**, 38662-43-0; **6**, 4663-22-3; **10a**, 38662-44-1; **10b**, 38662-45-2; **11**, 825-76-3; **12**, 38661-79-9; **14**, 38661-80-2; benzyne, 462-80-6.

Acknowledgment.—We are thankful to Professor Lester Friedman of the Case Western Reserve University Department of Chemistry, Cleveland, Ohio, for suggesting the topic while here as a guest professor in 1971, and for his help at the earlier stage of this work. We also wish to thank Dr. Joseph Deutsch of this department for his kind help and valuable comments.

The Allylic Rearrangement. III.[1,2] A Favorskii-Type Rearrangement of the Vinylogs of α-Chloroacetones

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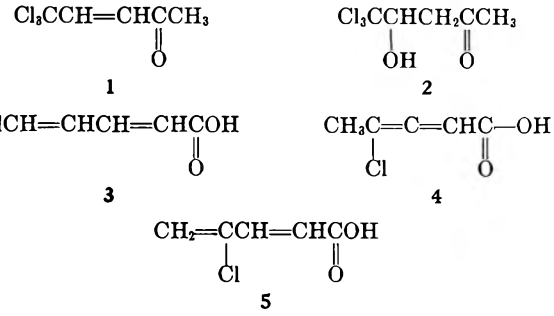
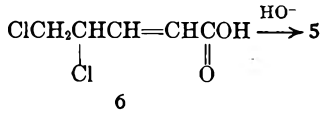
A Favorskii-type rearrangement of the vinylogs of α-chloroacetones is described. The alkaline hydrolysis of 5,5,5-trichloro-3-penten-2-one (1) or its precursor, 5,5,5-trichloro-4-hydroxy-2-pentanone (2), gave 5-chloro-2,4-pentadienoic acid (3) in a 27–29% yield. The treatment of 1 with methanolic sodium methoxide gave the mixture of the methyl ester (10) of 3 and the methyl ester (14) of 5,5-dichloro-4-pentenoic acid (13). The alkaline hydrolysis of 5,5-dichloro-3-penten-2-one (7), 5,5-dichloro-3-hexen-2-one (8), and 5,5-dichloro-4-hydroxypentan-2-one (9) also gave the corresponding unsaturated acids. The reactions carried out in protic solvents tend to afford 4-pentenoic acid derivatives predominantly rather than 2,4-pentadienoic acid derivatives. It is assumed that the pathway of the formation of 3 from the starting material 1 involves a Favorskii-type rearrangement initiated by loss of chlorine at C-5 from the enolate anion of 1 to give a dipolar ion intermediate.

It has long since been known that the alkaline hydrolysis of 5,5,5-trichloro-3-penten-2-one (1)[3] or 5,5,5-trichloro-4-hydroxy-2-pentanone (2)[4] gives a carboxylic acid (3) with the composition of $C_5H_5O_2Cl$, mp 171–172°. Uschakow[4] once assigned the structure of 4-chloro-2,3-pentadienoic acid (4) and/or 4-chloro-2,4-pentadienoic acid (5) to the acid. On the other hand,



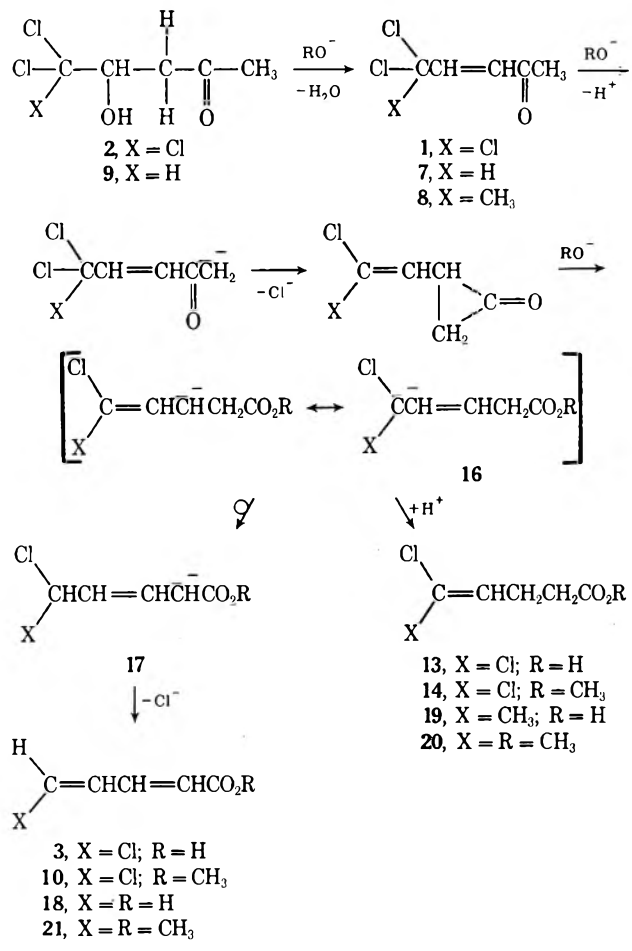
Muskat has later shown that the latter structural assignment of Uschakow was not correct, as he obtained the real acid 5, which melted at about 94°,[5] by the alkaline dehydrochlorination of 4,5-dichloro-2-pentenoic acid (6). The structure of the acid 3 had been



left ambiguous thereafter. In the course of our study on the reactions of the pentenone 1,[2,6] we became interested in reexamining the structure of the acid 3 and have identified it as 5-chloro-2,4-pentadienoic acid.

We assumed the pathway of the formation of 3 from the starting material 1 to involve a Favorskii-type rearrangement initiated by loss of chlorine at C-5 from the enolate anion[7] of 1 as shown in Scheme I. To ensure the validity of this assumption, we carried out the alkaline hydrolysis of a number of substrates with the structures of the vinylog of α-chloroacetones such as 5,5-dichloro-3-penten-2-one (7) and 5,5-dichloro-3-hexen-2-one (8) or the precursor of 7, 5,5-dichloro-4-hydroxypentan-2-one (9). These compounds also afforded the unsaturated carboxylic acids, whose formation can be well explained by the proposed mechanism. This paper describes the structural identification of the acid 3 and the related compounds and discusses the reaction mechanisms of their formation.

SCHEME I



Results and Discussion

By the alkaline hydrolysis of either 1 or 2, we obtained the acid, mp 170°, in a 19–29% yield, which was

(1) Presented in part at the 24th Annual Meeting of the Chemical Society of Japan, Osaka, Japan, April 1, 1971.

(2) Preceding paper: A. Takeda, S. Tsuboi, T. Moriwake, and E. Hirata, *Bull. Chem. Soc. Jap.*, **45**, 3685 (1972).

(3) I. Salkind, *J. Russ. Phys. Chem. Soc.*, **30**, 906 (1898).

(4) S. P. Uschakow, *ibid.*, **29**, 113 (1897).

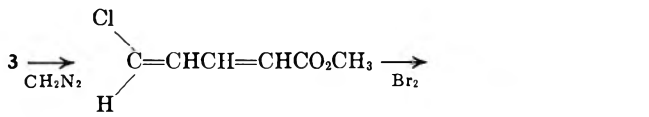
(5) I. E. Muskat and B. C. Becker, *J. Amer. Chem. Soc.*, **52**, 812 (1930). Owing to its ease of polymerization it was not possible for these authors to get a sharp melting point.

(6) A. Takeda and S. Tsuboi, *J. Org. Chem.*, **35**, 2690 (1970).

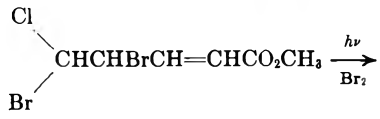
(7) It appears that Favorskii rearrangements generally involve ionization of halide ion from the initially formed enolate ion to give a dipolar ion intermediate, which then collapses to a cyclopropanone: F. G. Bordwell, R. G. Scamehorn, and W. R. Springer, *J. Amer. Chem. Soc.*, **91**, 2087 (1969); F. G. Bordwell and R. G. Scamehorn, *ibid.*, **93**, 3410 (1971). Applied to compound 1 this mechanism predicts the formation of dipolar ion $Cl_2C{=}CH{-}{}^{+}CHCO\bar{C}H_2{}^{-}$, which then gives the cyclopropanone shown in Scheme I.

believed to be the same one as that described by Uschakow.[4] The mass spectrum of this product as well as its analyses supported the composition $C_5H_5O_2Cl$. The ir spectrum (KBr) of the acid **3** exhibited absorptions at 3060 (>C=CH), 3000–2500 (carboxy), 1690 and 1670 (conjugated carboxy C=O), 1655 (shoulder, C=C), 1620 (C=C), 1002 and 950 (trans HC=CH), 840 (cis HC=CH), and 710 cm^{-1} (CCl). The allenic structure can be ruled out from the possible structures of **3** because no notable absorption was observed in the region of 1950 cm^{-1}. Since the nmr spectrum [d, $(CD_3)_2CO$] showed signals due to four vicinally coupled protons attached to the individual carbon atoms, 5-chloro-2,4-pentadienoic acid has now been assigned to this product (**3**).[8] The geometry of the acid **3**, trans-2:cis-4, is estimated by the coupling constants observed of four protons[9] and also by the ir absorptions in the region of 800–1000 cm^{-1}.[10] No additional peaks ascribable to other isomers were observed.

The acid **3** was converted to the methyl ester **10** with diazomethane quantitatively. One mole of the ester **10** took 2 mol of bromine in two steps. In addition to the acid **3**, 5,5-dichloro-4-pentenoic acid (**13**, 19%)



10



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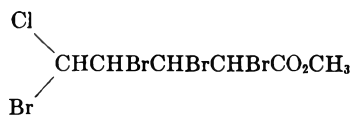
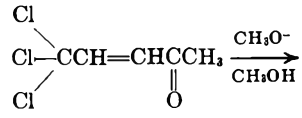


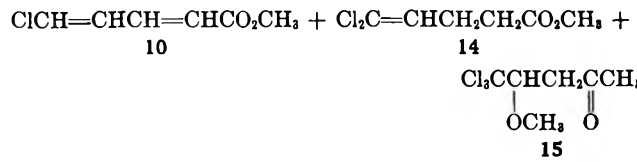
12

that Uschakow[4] did not allude to was obtained in the alkaline hydrolysis of **1**. The acid **13** was converted to the methyl ester **14**. The nmr spectrum of **14** in carbon tetrachloride showed one olefinic proton as a triplet at δ 5.89 ppm, methyl ester protons as a singlet at 3.64 ppm, and methylene protons as a multiplet centered at 2.41 ppm. The mass spectrum of **14** showed strong molecular ions at *m/e* 182 with the characteristic chlorine isotope distribution.

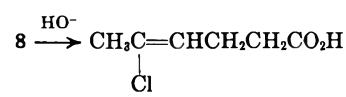
The treatment of **1** with methanolic sodium methoxide at 20–25° for 10 min gave the mixture of esters **10** and **14** and 5,5,5-trichloro-4-methoxypentan-2-one (**15**).[2] Only the ester **10** was isolated when **1** was treated with sodium methoxide in ether. The derivation of **13** and **14** in hydroxylic solvents can be explained by assuming a delocalized anion **16**, which, in protic solvents, is thought to give protonated products



1

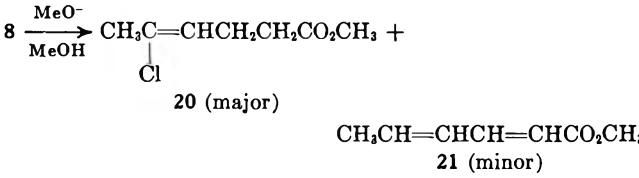


partly and isomerized products partly. The latter products probably underwent a dehydrochlorination to give **3** and **10**. This mechanism is further substantiated by the reaction of dichloro ketones **7**, **8**, and **9** with base. By treatment with aqueous sodium hydroxide, both **7** and **9** were converted to *trans*-2,4-pentadienoic acid (**18**)[11] in a 25% yield. The alkaline hydrolysis of the ketone **8** afforded 5-chloro-4-hexenoic acid (**19**)[12] exclusively in a 27% yield. The ir bands



19

at 1700 (acid C=O) and 1660–1630 cm^{-1} (C=C) indicated the α,β-saturated structure of **19**. The unusually high δ value of its methylene protons (broad singlet, 2.42 ppm) is due to deshielding effects of the acid group and the vinyl group. The transformation of an intermediate **16** to **17** appears to be more favored when the substituent X is chlorine or hydrogen, since ketones **1**, **2**, **7**, and **9** afforded 2,4-pentadienoic acid derivatives as main products in protic solvents, whereas the ketone **8** gave 4-hexenoic acid derivatives as main products in protic solvents. When **8** was treated with sodium methoxide in dry methanol, the methyl ester **20**[13a] of the acid **19** was produced as the major component



20 (major)

21 (minor)

along with methyl sorbate (**21**)[13b] as the minor component. The ester **20** was transformed to methyl sorbate (**21**) by the action of sodium methoxide in ether, though in a low yield (6%). This fact presents additional evidence to support the proposed mechanism of the Favorskii-type rearrangement reported here. The reaction sequence of **20** is given in Scheme II.

The effect of aprotic solvents on the product distribution has been further investigated. Table I summarizes the results of the reactions which were carried out in aprotic solvents such as ether, benzene, and *n*-hexane, and also those in protic solvents. There is an indication that the reactions in protic solvents afford more 4-alkenoic acid as compared to those in aprotic

(8) Two monochloropentadienoic acid structures, i and ii, have two geminate protons. Compound ii has been derived by Corre, *et al.*, by the

i ii

reaction of 2,3,3-trichloropropenal with vinylmagnesium chloride: M. L. Corre and E. Levas, *C. R. Acad. Sci., Ser. C*, **260**, 3414 (1965); lit. mp 118–119°.

(9) Y. Leraux and E. Vauthier, *C. R. Acad. Sci., Ser. C*, **271**, 1333 (1970).

(10) (a) L. Crombie, *J. Chem. Soc.*, 1007 (1955); (b) J. L. H. Allan, G. D. Meakins, and M. C. Whiting, *ibid.*, 1874 (1955).

(11) H. O. House and G. H. Rasmusson, *J. Org. Chem.*, **26**, 4278 (1961). The geometry of **18**, trans-2, is estimated by the coupling constant ($J_{2,3}$ = 14.8 Hz).

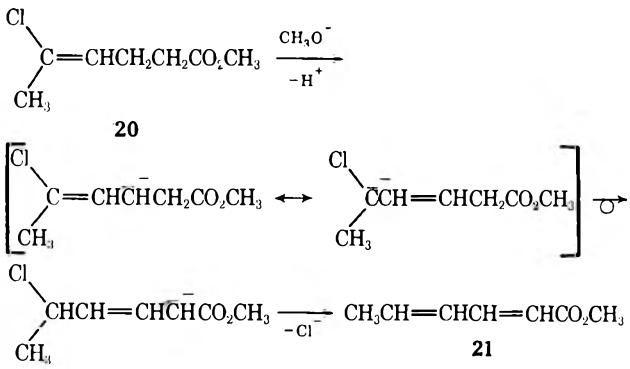
(12) Cis,trans mixture (3:7, or 7:3). Glpc analysis of its methyl ester (**20**) showed the presence of two components, which differed slightly in ir spectra at *ca.* 1340 and 790–800 cm^{-1}.

(13) (a) Cis,trans mixture (1:6 or 6:1). (b) The ir and nmr data indicate the geometry of this product to be trans-2:trans-4.[10]

TABLE I
REARRANGEMENT PRODUCTS FROM THE REACTION OF KETONES WITH BASE IN VARIOUS SOLVENTS

Ketone, $XCCl_2CH{=}CHCOCH_3$ or $XCCl_2CH(OH)CH_2COCH_3$ Compd	X	Base (RO^-) R	Solvent	Yield of rearrangement products, % $XCCl{=}CHCH_2CH_2CO_2R$	Yield of rearrangement products, % $XCH{=}CHCH{=}CHCO_2R$
1	Cl	H	Water	19 (13)	29 (3)
1	Cl	CH_3	Methanol	4 (14)	32 (10)
2	Cl	H	Water	0	27 (3)
1	Cl	CH_3	Ether	0	10 (10)
9	H	H	Water	0	25 (18)
7	H	H	Water	0	25 (18)
8	CH_3	H	Water	27 (19)	0
8	CH_3	CH_3	Methanol	34 (20)	17 (21)
8	CH_3	CH_3	Ether	5 (20)	9 (21)
8	CH_3	CH_3	Benzene	16 (20)	39 (21)
8	CH_3	CH_3	*n*-Hexane	1 (20)	21 (21)

SCHEME II



solvents, probably as a result of protonation of the intermediate **16**.

Experimental Section

The melting points and boiling points are uncorrected. Elemental analyses were carried out by Mr. Eiichiro Amano of our laboratory and microanalysis of chlorine content is due to Mr. Tsunekazu Kirido of Kuraray Co. Ltd., Kurashiki, Japan. Analytical determinations by glpc were performed on a Hitachi Model K-53 gas chromatograph fitted with the following columns (3 mm o.d. × 1 m): A, 10% Apiezon grease L on Chromosorb W; B, 10% polyneopentyl glycol succinate on Chromosorb W; C, 10% SE-30 on Chromosorb W. The preparative isolations by glpc were performed on a Yanagimoto Model GCG-550T gas chromatograph (3 mm o.d. × 2.25 m, 10% Apiezon Grease L on Chromosorb W). Mass spectra were obtained with a Hitachi Model RMS-4 mass spectrometer. We are indebted to Mr. Hiroshi Ooyama, Hokko Chemical Industry Co., Ltd., and Mr. Heizan Kawamoto and Miss Hiromi Ootani for nmr (60 MHz) measurements. Microanalyses and spectral measurements of liquid substances were performed on the samples collected by glpc or tlc.

5,5,5-Trichloro-4-hydroxy-2-pentanone (**2**)[6,14] and 5,5,5-trichloro-3-penten-2-one (**1**)[3,6] were prepared in ways similar to those described in the literature. Sorbic acid of commercial grade was purified by recrystallization from hot water, mp 133–134° (lit.[15] mp 134°). 2,4-Pentadienoic acid was prepared by the method described in the literature,[11] mp 69–70° (lit.[11] mp 71.5–72.5°).

5-Chloro-2,4-pentadienoic Acid (3).—To 165 ml of 12% sodium hydroxide cooled in an ice bath was added with stirring 102 g (0.50 mol) of **2** in one portion. When most of **2** came to solution the ice bath was removed. After the reaction mixture was allowed to come to room temperature, 165 ml of 12% sodium hydroxide was added. After the temperature was decreased to room temperature an additional amount (165 ml) of 12% sodium hydroxide was added. The mixture was heated for several minutes at 50–60°, treated with activated charcoal, and finally acidified with dilute hydrochloric acid to pH 2. The solid was collected, thoroughly washed with water, and air dried to give 18 g (yield 27%) of crude **3**. Recrystallization from chloroform gave 9 g (14%) of **3**: mp 170°; ir (KBr) 3060 (C=CH), 3000–2500 (COOH), 1690 (acid C=O), 1670 (acid C=O), 1620 (C=C), 1330, 1002, 952, 833, 710 cm^{-1}; nmr [$(CD_3)_2CO$] δ 6.02 (d, 1, J = 14.3 Hz, $-CH{=}CHCO_2H$), 6.82 (d, 1, J = 11.4 Hz, $ClCH{=}CH-$), 6.95 (dd, 1, J = 11.4 and 10.4 Hz, $ClCH{=}CH-$), 7.37 ppm (dd, 1, J = 10.4 and 14.3 Hz, $-CH{=}CHCO_2H$); mass spectrum (70 eV m/e (rel intensity) 132 (23, M^+, 1 Cl), 115 (5), 97 (100), 89 (7), 87 (21), 79 (8), 69 (24), 61 (10), 51 (77), 50 (27), 49 (9), 44 (13), 43 (9), 41 (60), 39 (19), 38 (14), 36 (42).

Anal. Calcd for $C_5H_5ClO_2$: C, 45.30; H, 3.80; Cl, 26.71. Found: C, 45.28; H, 3.92; Cl, 26.82.

Methyl 5-Chloro-2,4-pentadienoate (10).—Acid **3** (4.4 g, 0.033 mol) was esterified with diazomethane as usual to give 4.5 g (94%) of **10**: bp 66° (5 mm); mp 43–43.5° (*n*-hexane); ir (neat) 3060 (C=CH), 2960, 1720 (ester C=O), 1630 (C=C), 1585 (C=C), 1440, 1320, 995, 840, 730 cm^{-1} (CCl); nmr (CCl_4) δ 3.69 (s, 3, CO_2CH_3), 5.87 (d, 1, J = 14 Hz, $=CHCO_2CH_3$), 6.28–6.90 (m, 1, $-CH{=}CHCO_2CH_3$), 6.48 (d, 1, $ClCH{=}CH-$), 7.19 ppm (m, 1, $ClCH{=}CH-$).

Anal. Calcd for $C_6H_7ClO_2$: C, 49.17; H, 4.81. Found: C, 49.10; H, 4.82.

Alkaline Hydrolysis of 1.—Similar treatment of **1** (3.2 g, 0.016 mol) with 36 ml of 12% aqueous sodium hydroxide gave 0.34 g of crude **3**, as in the case of compound **2**. The extraction of the filtrate with ether gave 0.79 g of light brown needles. Tlc analysis of this product showed two spots, but the separation of these components by tlc was not successful. The esterification of the solid with diazomethane afforded a light brown oil. Glpc analysis (column A, 120°, carrier gas N_2, 0.5 kg/cm^2, 42 ml/min) showed two peaks, with retention times of 7.8 and 9.6 min, respectively, and in an area ratio of 34:66. Components 1 and 2 were collected by preparative glpc and identified as **10** (yield 29%[16]) and methyl 5,5-dichloro-4-pentenoate (**14**) (yield 19%), respectively, by comparison of ir spectrum and retention time with those of authentic samples.[17]

Reaction of 1 with Sodium Methoxide in Dry Methanol.—To a stirred solution of 17.3 g (0.32 mol) of sodium methoxide in 60 ml of dry methanol was added dropwise a solution of 10 g (0.054 mol) of **1** in 20 ml of dry methanol, at 20–25° for a period of 15 min. The mixture was stirred for 10 min and poured into a large excess of water. The organic layer was extracted with ether. The ethereal extracts, treated with activated charcoal, were washed with water and dried over $MgSO_4$. Removal of the solvent left 5.5 g of a clean oil. Glpc analysis (column C, 130°, carrier gas N_2, 0.5 kg/cm^2, 42 ml/min) of this oil showed four peaks. The peaks, retention times (min), and integrated percentages are as follows: 1, 1.8, 46%; 2, 2.7, 7%; 3, 3.2, 6%; 4, 3.8, 38%. Each component was collected by preparative glpc. Component 1, which solidified in a few minutes after separation, was identified as ester **10**, mp 41.5–42° after one recrystallization from *n*-hexane, yield 32%.

Component 2 was identified as **14**: yield 4%; ir (neat) 1735 (ester C=O), 1620 (C=C), 1438, 1175, 890 cm^{-1}; nmr (CCl_4) δ 2.41 (m, 4, $-CH_2CH_2CO_2CH_3$), 3.64 (s, 3, $-CO_2CH_3$), 5.89 ppm

(14) H. Gault and G. Mennicken, *C. R. Acad. Sci. Ser. C*, **229**, 1239 (1949).

(15) C. F. H. Allen and J. Van Allan, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 783.

(16) Total yield of **3**.

(17) For spectral data of compound **14** see the next section.

(t, 1, J = 8 Hz, =CH–); mass spectrum (70 eV) m/e (rel intensity) 182 (52, M^+, 2 Cl), 151 (70, 2 Cl), 147 (100, 1 Cl), 124 (87), 122 (95), 115 (53), 109 (84), 105 (41), 87 (75), 59 (65), 51 (61), 43 (40).

Anal. Calcd for $C_6H_8Cl_2O_2$: C, 39.37; H, 4.40. Found: C, 39.50; H, 4.54.

Component **4** was identified as **15** by comparison of ir and retention time with those of the authentic sample,[2] yield 18%.

Reaction of 1 with Sodium Methoxide in Dry Ether.—To a solution of 5 g (0.027 mol) of **1** in 30 ml of dry ether, 2.9 g (0.053 mol) of sodium methoxide was added slowly at −60 to −50°. The mixture was stirred for 30 min at −60 to −50° and then for 20 min at −40 to −30°. The mixture was poured into ice water and acidified with dilute hydrochloric acid. The organic layer was extracted with ether several times. The extracts were dried over Na_2SO_4. Removal of the solvent left a deep brown oil which, on distillation, gave 0.4 g (10%) of a clean oil, bp 65–68° (6 mm). It was identified as **10** by comparison of retention time and ir spectrum with those of the sample synthesized in the previous section.

Methyl 4,5-Dibromo-5-chloro-2-pentenoate (**11**).—To a solution of 6.3 g (0.043 mol) of **10** in 30 ml of dry carbon tetrachloride was added 6.9 g (0.043 mol) of bromine at 20°. After the mixture had been stirred for 2 hr, it was allowed to stand overnight at room temperature. Removal of the solvent left a brown oil which, on distillation, gave 10.6 g (81%) of **11**: bp 125–133° (5 mm); ir (neat) 3030, 1725 (ester C=O), 1655 (C=C), 1440, 1290, 980, 735 cm^{-1} (CCl); nmr (CCl_4) δ 3.77 (s, 3, CO_2CH_3), 4.95 (m, 1, –CHBrCH=), 5.88 (d, 1, J = 5.9 Hz, ClBrCH), 6.10 (d, 1, J = 13 Hz, $=CHCO_2CH_3$), 6.98 (m, 1, $-CH=CHCO_2CH_3$); mass spectrum (70 eV) m/e (rel intensity) 274 (0.4, $M^+ - CH_3OH$), 244 (1), 225 (24), 189 (14), 165 (6), 145 (13), 115 (58), 111 (100), 87 (85), 59 (65), 51 (73).

Anal. Calcd for $C_6H_7Br_2ClO_2$: C, 23.52; H, 2.30. Found: C, 23.30; H, 2.57.

Methyl 2,3,4,5-Tetrabromo-5-chloropentanoate (**12**).—To a solution of 2 g (0.014 mol) of **10** in 20 ml of dry carbon tetrachloride was added 4.6 g (0.029 mol) of bromine at 0°. The mixture was stirred at room temperature for 2 days under the irradiation of the ultraviolet lamp. Removal of the solvent left a yellow oil which, on distillation under an atmosphere of nitrogen, yielded 2.2 g (35%) of **12**: bp 153–154° (3 mm); mp 133–135° (*n*-hexane); ir (Nujol) 1750 cm^{-1} (ester C=O).

Anal. Calcd for $C_6H_7Br_4ClO_2$: C, 15.43; H, 1.51. Found: C, 15.73; H, 1.69.

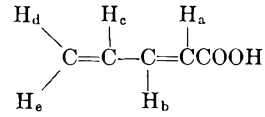
5,5-Dichloro-4-hydroxypentan-2-one (**9**).—This material was prepared by the literature procedure for the synthesis of chloral-acetone (**2**)[14] with a slight modification. A mixed solution of 22.8 g (0.17 mol) of ethyl acetoacetate in dilute aqueous potassium hydroxide prepared from 12 g (0.21 mol) of potassium hydroxide and 460 ml of water was stirred at room temperature for 1 day. After the mixture was acidified with 10% hydrochloric acid, a solution of 18.4 g (0.16 mol) of dichloroacetaldehyde in 28 ml of water was added. The mixture was stirred for 3 days. The pH of the solution was adjusted to 5 by adding 10% hydrochloric acid when necessary. After evaporation of two-thirds of the water, the residual oil was extracted with ether and the extract was dried over Na_2SO_4. Removal of the solvent left a clean oil which, on distillation, gave 14.2 g (52%) of **9**: bp 121–123° (0.1 mm); ir (neat) 3400 (OH), 1710 (C=O), 1425, 1370, 1090, 755, 735, 705 cm^{-1}; nmr ($CDCl_3$) δ 2.26 (s, 3, $COCH_3$), 2.92 (d, 2, J = 5.5 Hz, $-CH_2COCH_3$), 3.58 (s, 1, OH), 4.42 (dt, 1, J = 4 and 5.5 Hz, >CHOH), 5.85 (d, 1, J = 4 Hz, $-CHCl_2$).

Anal. Calcd for $C_5H_8Cl_2O_2$: C, 35.11; H, 4.71. Found: C, 34.83; H, 4.80.

5,5-Dichloro-3-penten-2-one (**7**).—To 17 ml of concentrated sulfuric acid was added 1.7 g (0.01 mol) of **9** at room temperature. The mixture was allowed to stand for 2.5 hr and poured onto cracked ice. The organic layer was extracted with ether several times and the combined extracts were dried over Na_2SO_4. Removal of the solvent left a pale brown oil, which on distillation under an atmosphere of nitrogen gave 1.0 g (65%) of a clean oil (**7**): bp 91–92° (17 mm), ir (neat) 3030, 1710–1660 (C=O), 1640 (C=C), 730 cm^{-1}; nmr (CCl_4) δ 2.3 (s, 3, $COCH_3$), 6.22 (d, 1, J = 15.8 Hz, $=CHCOCH_3$), 6.23 (d, 1, J = 6.4 Hz, $-CHCl_2$), 6.78 ppm (dd, 1, J = 6.4 and 15.8 Hz, $CHCl_2CH=$); mass spectrum (70 eV) m/e (rel intensity) 152 (13, M^+, 2 Cl), 137 (100, $M^+ - CH_3$, 2 Cl), 117 (9, $M^+ - Cl$, 1 Cl), 109 (48, $M^+ - CH_3CO$, 2 Cl).

Anal. Calcd for $C_5H_6Cl_2O$: C, 39.25; H, 3.95. Found: C, 39.62; H, 3.85.

trans-**2,4-Pentadienoic Acid** (**18**). **A. From 9.**—Hydroxypentanone **9** (2.1 g, 0.012 mol) was added to 4.4 ml of 10% sodium hydroxide at room temperature. The mixture was heated at 60° for 5 min, and then was treated with activated charcoal. The filtrate was acidified with 10% hydrochloric acid. The organic layer was extracted with ether several times and the extracts were dried over Na_2SO_4. Removal of the solvent left 0.3 g (25%) of light brown needles (**18**), mp 68–70° (from ether) (lit.[11] mp 71.5–72.5°). Ir and nmr spectra were identical with that of an authentic sample:[11] ir (Nujol) 2900–2500 (COOH),



1690 (C=O), 1630, and 1600 cm^{-1} (C=C); nmr ($CDCl_3$) δ 5.60 (dd, 1, J = 1.6 and 17.2 Hz, H_e), 5.69 (dd, 1, J = 1.6 and 9.4 Hz, H_d), 5.90 (d, 1, J = 14.8 Hz, H_a), 6.50 (dt, 1, J = 9.6 and 17.2 Hz, H_c), 7.38 ppm (dd, 1, J = 9.6 and 14.8 Hz, H_b).

B. From 7.—Pentenone **7** (2.5 g, 0.016 mol) was added to 26 ml of 15% sodium hydroxide and the mixture was stirred for 5 min. After being washed with ether and treated with activated charcoal, the aqueous layer (pH 11) was acidified with 10% hydrochloric acid. The acidic material was extracted with ether three times and the ethereal extracts were dried over Na_2SO_4. Removal of the solvent left 0.7 g of pale brown needles. The fractionation of this product by means of preparative tlc[18] gave 0.4 g (25%) of pale yellow needles of **18**, mp 68–70°. The ir and nmr spectra were identical with those of a pure sample obtained from **9**.

5,5-Dichloro-3-hexen-2-one (**8**).[19]—To a mixed solution of 12.1 g (0.095 mol) of freshly distilled 2,2-dichloropropanal[20] and acetylacetone (10 g, 0.1 mol) in 50 ml of dry THF was added 20.7 g (0.15 mol) of anhydrous potassium carbonate in several portions. After being stirred at room temperature for 1 day, the mixture was poured into 150 ml of water and acidified with 10% hydrochloric acid. The organic layer was extracted with ether and the ethereal extracts were washed with water and dried over Na_2SO_4. Removal of the solvent left a pale brown oil which, on distillation, gave 8.2 g (52%) of **8**: bp 77–80° (6 mm); ir (neat) 1710 and 1685 (conjugated C=O), 1638 (conjugated C=C), 1365, 1285, 1260, 1080, 980, 700, 685 cm^{-1} (CCl); nmr (CCl_4) δ 2.30 (s, 6, 2 CH_3), AB quartet centered at 6.30 and 6.88 ppm (2, J = 15 Hz, $-CH=CHCOCH_3$).

Anal. Calcd for $C_6H_8Cl_2O$: C, 43.15; H, 4.83. Found: C, 43.18; H, 4.97.

5-Chloro-4-hexenoic Acid (**19**).—To 36 ml of 15% sodium hydroxide was added the ketone **8** (4.2 g, 0.027 mol), with stirring at 50°. After being stirred at 70–75° for 4 min, the mixture was cooled, washed with ether to remove neutral materials, and acidified with 10% hydrochloric acid. The organic layer was extracted with ether several times, and the ethereal extracts were dried over $MgSO_4$. The solvent was removed *in vacuo*, and the residue, on distillation, gave 1.1 g (27%) of **19**: bp 105–108° (3 mm); ir (neat) 2650 (COOH), 1700 (C=O), 1660–1630 cm^{-1} (shoulder, C=C); nmr ($CDCl_3$) δ 2.09 (s, 3, $CH_3CCl=$), 2.42 (broad s, 4, $-CH_2CH_2-$), 5.50 (broad t, 1, J = 4 Hz, =CH–), 11.30 ppm (s, 1, COOH); mass spectrum (70 eV) m/e (rel intensity) 148 (64, M^+, 1 Cl), 131 (7, $M^+ - CH_3$), 113 (100, $M^+ - Cl$), 102 (70), 95 (56), 91 (70), 89 (83), 71 (72), 67 (71), 60 (62), 53 (71).

Anal. Calcd for $C_6H_9ClO_2$: C, 48.50; H, 6.10. Found: C, 48.61; H, 6.28.

Methyl 5-Chloro-4-hexenoate (**20**).—Esterification of **19** with diazomethane afforded the ester **20**, bp 55° (5 mm). Glpc analysis (column A, 120°, carrier gas, N_2, 0.5 kg/cm^2, 42 ml/min) showed two peaks. The peaks, retention times (min), and integrated percentages are as follows: 1, 4.2, 70%; 2, 4.9, 30%.

(18) Conditions of preparative tlc: support, silica gel G (E. Merk AG, Darmstadt), 0.8 mm; developer, benzene–acetic acid–methanol (10:1:1 v/v); R_f 0.67.

(19) This procedure to prepare 3-alken-2-one from acetylacetone and α-halogenoaldehydes has been explored by one of us (A. T.) recently: A. Takeda and T. Uno, to be published.

(20) 2,2-Dichloropropanal was prepared by the chlorination of propanal with chlorine by the method of Dick: C. R. Dick, *J. Org. Chem.*, **27**, 272 (1962).

Component 1 was collected by preparative glpc and identified as *trans*-**20** (or *cis*-**20**): ir (neat) 1740 (ester C=O), 1660 (C=C), 1440, 1366, 1175, 1110, 1040, 990, 830, 790 cm^{-1}; nmr (CCl_4) δ 2.08 (s, 3, CH_2CCl=), 2.33 (broad s, 4, $-CH_2CH_2$), 3.62 (s, 3, $-CO_2CH_3$), 5.51 ppm (broad s, 1, -CH=); mass spectrum (70 eV) *m/e* (rel intensity) 162 (19, M^+, 1 Cl), 131 (76), 127 (100, $M^+ - Cl$), 105 (61), 104 (60), 103 (68), 102 (75), 95 (57), 89 (72), 85 (68), 74 (61), 67 (63), 59 (50), 53 (61).

Anal. Calcd for $C_7H_{11}ClO_2$: C, 51.70; H, 6.82. Found: C, 51.58; H, 6.72.

Component 2, collected similarly, was identified as *cis*-**20** (or *trans*-**20**): ir (neat) 1740 (ester C=O), 1660 (C=C), 1440, 1366, 1340, 1175, 1110, 1080, 1035, 990, 860, 830, 800 cm.$^{-1}$ The nmr (CCl_4) and mass spectrum (70 eV) of this component were like those of component 1.

Anal. Calcd for $C_7H_{11}ClO_2$: C, 51.70; H, 6.82. Found: C, 51.43; H, 6.60.

Reaction of 8 with Sodium Methoxide in Dry Methanol.—To a stirred solution of 5.9 g (0.11 mol) of sodium methoxide in 25 ml of dry methanol was added dropwise at 34–45° a solution of **8** (3 g, 0.018 mol) in 6 ml of dry methanol, for a period of 10 min. The mixture was stirred for additional 15 min, and poured into a large amount of water. The organic layer was extracted with ether, washed with water, and dried over $MgSO_4$. Removal of the solvent left 1.4 g of a light yellow, clean oil, bp 75–78° (12 mm). Glpc analysis (column B, 120°, carrier gas N_2, 0.5 kg/cm², 42 ml/min) of this oil showed three peaks. The peaks, retention times (min), and integrated percentages are as follows: 1, 3.2, 28%; 2, 4.7, 60%; 3, 6.2, 11%. Component 1 was collected by preparative glpc and identified as methyl sorbate (**21**) by comparison of the infrared spectrum and retention time with those of methyl sorbate prepared by the esterification of sorbic acid with diazomethane: yield 17%; ir (neat) 1723 (ester C=O), 1650 (C=C), 1623 (C=C), 1010 cm^{-1} (=CH);[10] nmr (CCl_4) δ 1.85 (d, 3, J = 5.5 Hz, $-CH_3$), 3.67 (s, 3, $-CO_2CH_3$), 5.69 (d, 1, J = 16 Hz, C-2 H), 6.20 (m, 2, C-4 H and C-5 H), 7.16 ppm (m, 1, C-3 H).[9]

Components 2 and 3 were collected and identified as *trans*-**20** (or *cis*-**20**) (yield 29%) and *cis*-**20** (or *trans*-**20**) (yield 5%), respectively, by comparison of ir spectra and retention times with those of an authentic sample.

Reaction of 8 with Sodium Methoxide in Aprotic Solvents (Ether, Benzene, and *n*-Hexane).—To a suspension of 0.76 g (0.014 mol) of sodium methoxide in 10 ml of aprotic solvent was added 0.88 g (0.0048 mol) of **8** in several portions during the course of 5 min, at 0° with stirring. After the mixture was stirred at 0–10° for a further 30 min, it was worked up in the usual manner. The composition of the products was determined by glpc (column B, 120°, carrier gas N_2, 0.5 kg/cm², 42 ml/min).

Transformation of the Ester 20 to the Ester 21 with Sodium Methoxide.—To a mixture of sodium methoxide (0.14 g, 0.0025 mol) and dry ether (1 ml) was added a solution of **20** (0.082 g, 0.0005 mol) in dry ether (1 ml) at 0°. The mixture was stirred for 30 min and filtered. Removal of the solvent gave 0.04 g of a clean oil. Glpc analysis (column A, 120°, carrier gas N_2, 0.5 kg/cm², 42 ml/min) indicated this oil to contain three components, which were identified by the comparison of the retention times with those of the authentic samples. Peaks, compounds, retention times (min), and the integrated peak areas are as follows: 1, **21**,[21] 3.3, 9%; 2, *trans*-**20** (or *cis*-**20**), 4.2, 61%; 3, *cis*-**20** (*trans*-**20**), 5.1, 30%.

Registry No.—**1**, 1552-26-7; **2**, 1552-33-6; **3**, 22970-18-9; **7**, 38666-05-6; **8**, 38666-06-7; **9**, 38666-07-8; **10**, 38666-08-9; **11**, 38666-09-0; **12**, 38666-10-3; **14**, 38666-11-4; **18**, 21651-12-7; **19**, 38666-13-6; (*Z*)-**20**, 38666-14-7; (*E*)-**20**, 38666-15-8; **21**, 1515-80-6; ethyl acetoacetate, 141-97-9; dichloroacetaldehyde, 79-02-7; acetylacetone, 123-54-6; 2,2-dichloropropanol, 27313-32-2.

(21) Yield 6%.

Determination of Stereochemistry in Vinyl Phosphorylated Species by Nuclear Magnetic Resonance Shift Reagents. Revised Mechanistic Pathways for the Perkow Reaction[1]

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The application of lanthanide induced shifts employing Eu(DPM)$_3$ [and, to a minor extent, Pr(DPM)$_3$], to the nmr spectra of di-, tri-, and tetrasubstituted vinyl phosphates, phosphonates, and phosphinates is described. Vicinal cis protons or methyl groups undergo greater shifts than the corresponding trans groups. On this basis, *E* and *Z* stereochemical assignments can be made for such groups. The major isomers in the *gem*-phenyl vinyl phosphorylated compounds featuring vicinal phenyl, methyl, bromine, or chlorine groups are shown to be *Z*, reversing our previous assignments. Confirmation of this assignment is found by a positive nuclear Overhauser effect from phenyl to vicinal proton on the major (*Z*) isomer of diethyl 1-phenyl-2-chlorovinylphosphate. Available stereochemical data, including these revised results and the tendency toward smaller *Z*/*E* ratios in Perkow reactions involving alkyl diphenylphosphinites, compared with trialkyl phosphites, are evaluated on the basis of variations of the carbonyl addition mechanism previously proposed. The Perkow reactions of α,α-dibromo ketones and α-bromo-α-phenyl ketones, which give only *Z* vinyl phosphorylated products, may occur *via* halogen attack. The importance of considering the magnitude of k_2 Br/Cl ratios for pairs of bromo and chloro ketones, as well as *E*,*Z* stereochemistry of the products, in evaluating the various mechanistic pathways for the Perkow reaction, is stressed.

We have recently reported the determination of the relative stereochemistry of the *E* and *Z* isomeric vinyl phosphates arising from the Perkow reaction of α-halo ketones with trialkyl phosphites,[2,3] Of the various methods used,[2] the most reliable *seemed* to be the use of nmr additive increments as developed by Simon and Sternhell[4] and modified by Tobey.[5] This method correctly assigns *E* and *Z* stereochemistry to isomeric di- and trisubstituted olefins in a large number of cases.

We now find that in the case of trisubstituted *gem*-phenyl vinyl phosphates (and the related phosphinates and phosphonates[6]) the *E* and *Z* assignments by

(1) This investigation was supported by Grant No. 19,664 from the National Science Foundation. This is Organophosphorus Chemistry. 23.

(2) I. J. Borowitz, S. Firstenberg, E. W. R. Casper, and R. K. Crouch, *J. Org. Chem.*, **36**, 3282 (1971).

(3) I. J. Borowitz, S. Firstenberg, G. B. Borowitz, and D. Schuessler, *J. Amer. Chem. Soc.*, **94**, 1623 (1972).

(4) (a) C. Pascual, J. Meier, and W. Simon, *Helv. Chim. Acta*, **49**, 164 (1966); (b) U. E. Matter, C. Pascual, E. Pretsch, A. Pross, W. Simon, and S. Sternhell, *Tetrahedron*, **25**, 691 (1969); (c) U. E. Matter, *et al.*, *ibid.*, **25**, 2023 (1969).

(5) S. W. Tobey, *J. Org. Chem.*, **34**, 1281 (1969).

(6) I. J. Borowitz and R. K. Crouch, *Phosphorus*, **3**, 3 (1973).

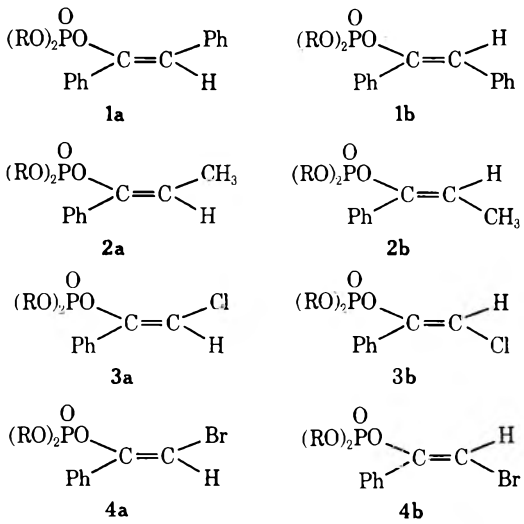
these calculations are close in value and give the reversed assignment; *i.e.*, the actual stereochemistry is the opposite (see below). If the correct assignments are compared with the calculated values (Table I),

TABLE I
CALCULATION OF VINYL PROTON NMR ABSORPTION IN *gem*-PHENYL VINYL PHOSPHATES[a]

Compd	Isomer	Vinyl proton [δ(CCl4)] Obsd	Calcd	
1a	Major, *Z*	6.33	6.49	(6.38)[b]
1b	Minor, *E*	6.69	6.33	
2a	Major, *Z*	5.60	5.60	(5.49)[b]
2b	Minor, *E*	5.77	5.35	
3a	Major,[c] *Z*	6.13	6.14	(6.03)[b]
3b	Minor,[c] *E*	6.45	5.96	
4a	Major, *Z*	6.14	6.18	(6.07)[b]
4b	Minor, *E*	6.49	5.93	

[a] R = C_2H_5. [b] Revised values using Z_{trans} = 0.61, based on **11b**, **13**, and **15**. Revision suggested by a referee. [c] Isomer ratio obtained in original Perkow reaction. Distillation reverses the isomer ratio.

the vinyl proton of the *E* isomers is found to be abnormally deshielded. Perhaps this is due to a decreased mesomeric effect of the phosphate group when it is part of a "buttressed" system (phosphate, *gem*-phenyl, R cis to phenyl) which does not allow the vinyl oxygen to be properly oriented for the usual shielding effect noted.[2]



1a **1b** **2a** **2b** **3a** **3b** **4a** **4b**

Allylic substitution next to a vinyl phenyl results in abnormal deshielding of vicinal vinyl protons, a related phenomenon.[4c]

In contrast, the additive increment method correctly predicts the nmr absorption of the vinyl protons in the *E*,*Z* isomeric pairs of substituted stilbenes containing morpholino[7a] and butyl[7b] groups (Table II). Thus stilbenes are not abnormal *per se*.

Determination of Vinyl Phosphate Stereochemistry by Lanthanide Induced Shifts (LIS).—The use of tris(dipivalomethanato)europium(III) [Eu(DPM)3] in causing lanthanide induced shifts in phosphates has been established.[8] It is generally agreed that the

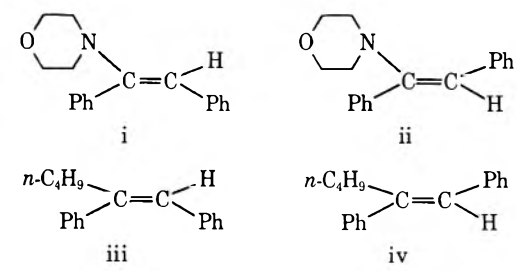
(7) (a) M. E. Munk and Y. K. Kim, *J. Org. Chem.*, **30**, 370 (1965); (b) J. E. Mulvaney, Z. G. Garlund, and S. L. Garlund, *J. Amer. Chem. Soc.*, **85**, 3897 (1963).

(8) (a) K. C. Yee and W. G. Bentrude, *Tetrahedron Lett.*, 2775 (1971); (b) R. von Ammon and R. D. Fischer, *Angew. Chem., Int. Ed. Engl.*, **11**, 675 (1972); (c) J. K. M. Sanders and D. H. Williams, *Tetrahedron Lett.*, 2813 (1971); (d) J. R. Corfield and S. Trippett, *Chem. Commun.*, 721 (1971).

TABLE II
CALCULATION OF VINYL PROTON NMR ABSORPTION IN STILBENES

Compd	Registry no.	Vinyl proton (δ) Obsd	Calcd[a]
i	4176-69-6	5.56[b]	5.32
ii	4176-68-5	5.71[b]	5.80
iii	5041-39-4	6.38[c]	6.36
iv	5041-40-7	6.64[c]	6.73

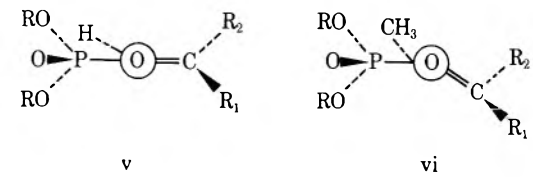
[a] From group increment values in ref 4b. [b] In cyclohexane.[7a] [c] In $CHCl_3$.[7b]



i ii iii iv

interaction involves coordination of the europium with the PO bond.[8a,c] Table III indicates LIS data obtained on di- and trisubstituted vinyl phosphates, phosphonates, and phosphinates. The data for compounds of known stereochemistry (the cyclic **5**–**9** and acyclic **10**–**12**) indicates the following order of decreasing proton sensitivity [shift, hertz/mole of Eu(DPM)3]: *gem*-vinyl H > cis *vic*-vinyl H ≅ CH_2 of ethoxy > trans *vic*-vinyl H ≧ CH_3 of ethoxy. The sensitivity values do not differ greatly for the various groups on phosphorus for a given ethylene. The values for genuine cis vicinal protons[2] (335 for **12**, 375 for **10**] are closer to the assigned cis vicinal proton in acyclic cases such as **11** or **16** than to the trans protons.[9]

These observations suggest that, at least in the presence of Eu(DPM)3, the vinyl phosphorylated species are either all in approximately the same geometrical configuration or that the same averaging of several configurations occurs in all cases. Inspection of Dreiding models indicates that, in most (but not all) of the possible rotational configurations for the PO group relative to the plane of the ethylene moiety, the cis vicinal proton is closer to it than is the trans vicinal proton. This is especially so for the preferred configurations v and vi for geminal pro-



v vi

ton and *gem*-methyl vinyl phosphates calculated by Gaydou from $^4J_{PH}$ coupling constants.[10] Although the exact position of the europium relative to the PO group is unknown, making the angular term in the usual shift equations[8b] difficult to evaluate, it seems reasonable that larger shifts will be associated with *vic*-vinyl protons which are cis to phosphate. The results for **1a** and **1b** (and dimethyl esters **20a** and **20b**) were confirmed with Pr(DPM)3 which gave greater upfield shifts for **20b** (Table III).

The method can be extended to tetrasubstituted

(9) The variation of the magnitude of LIS for H_{cis} (and other protons) with various structural features remains to be investigated.

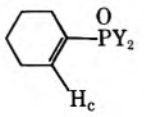
(10) E. Gaydou, *Tetrahedron Lett.*, 4473 (1972).

TABLE III

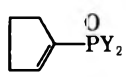
LANTHANIDE INDUCED SHIFTS IN PROTON NMR SPECTRA OF VINYL PHOSPHORYLATED SPECIES[a]

	Magnitude of induced shift (hertz/mole ratio)[b]							
	Vinyl proton							
Substrate	H_{cis}	H_{trans}	H_{gem}	POCH	POCCH	Other groups	$\Delta^{POCH}_{obsd}/\Delta^{i}_{obsd}$[c,d]	$\Delta^{POCCH}_{obsd}/\Delta^{i}_{obsd}$[c,d]
5, Y = OC_2H_5	487			488	176	412 (*gem*-CH_2)	1.01	0.36
6, Y = Ph	486							
7, Y = $OCH(CH_3)_2$	500			510	170	400 (*gem*-CH_2)	0.42	
8, Y = Ph	560					370 (*gem*-CH_2)		
9	510			510	170	400	1.00	0.33
10	375		710	570			H_c, 1.81	
							H_g, 0.82	
11a	300		592	525			H_c, 1.71	
							H_g, 0.94	
11b		75		545			H_t, 6.3	
12	335		710	565		22 (CCH_3)	H_c, 1.65	
13	528	192		486	168	304 (*gem*-CH_3)	H_c, 0.92	0.32
							H_t, 2.50	1.00
14, Y = Ph, OC_4H_9	736	184						
15, Y = OC_2H_5	650	180		500	175			
20a, Y = CH_3		225		400			1.66	
1a, Y = C_2H_5		280		580	153		1.99	0.59
20a		−360[e]		−580[e]			1.68	
20b	>225			610			0.67	
	−1220[e,f]			−810[e]			0.67	
16a, Y = Ph		210						
3a, Y = OC_2H_5		198		378	113			
16b, Y = Ph	470							
3b, Y = OC_2H_5	610			627	216			
4a,b, R = C_2H_5		248[g]		475[g]	152[g]			
2a, R = C_2H_5		140			140	260 (vinyl CH_3)		
2b, R = C_2H_5		440			120	40 (vinyl CH_3)		

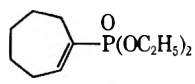
[a] The shifts are downfield and caused by Eu(DPM)$_3$ unless otherwise noted. [b] Obtained from the plots of δ *vs.* mole ratio of Eu(DPM)$_3$/substrate. [c] These ratios are obtained from the slopes of plots of LIS for POCH (or POCCH) *vs.* LIS for vinyl H or vinyl CH_3: D. R. Kelsey, *J. Amer. Chem. Soc.*, 94, 1764 (1972). [d] Similar ratios are obtained from the values listed in the table. [e] Pr(DPM)$_3$ values. [f] Eu(DPM)$_3$ with **1b** caused vinyl proton to merge with phenyl. [g] Values found on 97:3 mixture of **4a**:**4b**.



5, Y = OC_2H_5
6, Y = Ph



7, Y = $OCH(CH_3)_2$
8, Y = Ph



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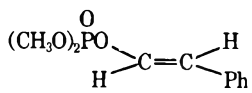

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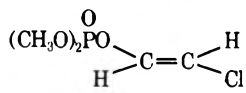
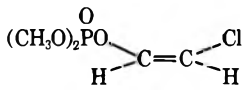


11a



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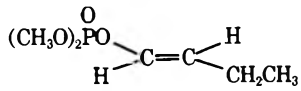

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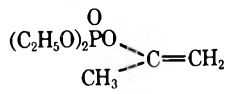

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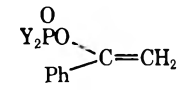
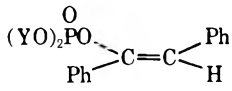
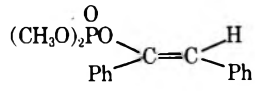


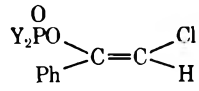
14, Y = Ph, OC_4H_9
15, Y = OC_2H_5



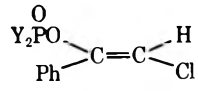
20a, Y = CH_3
1a, Y = C_2H_5



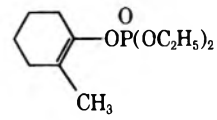
20b



16a, Y = Ph
3a, Y = OC_2H_5



16b, Y = Ph
3b, Y = OC_2H_5



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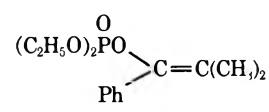

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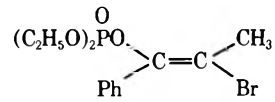
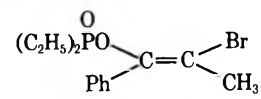


19a



19b

vinyl phosphates bearing methyl groups, whose stereochemistry is not otherwise readily accessible (Table IV). There is good agreement between the shift for the *cis*-methyl group in **17** and the assigned *cis*-methyl groups in **18** and **19**.

Thus the LIS method seems to represent a simple and powerful tool for the determination of *E*,*Z* stereochemistry in vinyl phosphorylated species.

Further Evidence for the Assignment of *E*,*Z* Stereochemistry of *gem*-Phenyl Vinyl Phosphorylated Species. —Since the stereochemistry of the *E*,*Z* pairs **1a,b**–**4a,b** as determined by LIS is opposite to that originally deduced by the Simon–Sternhell calculations,[2] further confirmation of the revised stereochemical assignments was sought. The diethyl 1-phenyl-2-chlorovinylphosphate pair **3** (60:40 ratio of distilled material, changed from the 40:60 ratio of isomers formed in the reaction of dichloroacetophenone with triethyl phosphite) has an upfield vinyl proton doublet which had been assigned as trans to phenyl originally.[2]

TABLE IV

Eu(DPM)$_3$ INDUCED SHIFTS ON VINYL METHYLS IN VINYL PHOSPHORYLATED SPECIES[a]

	Magnitude of induced shift (hertz/mole ratio)[b]						
	Vinyl methyl						
Substrate	*cis*-CH_3	*trans*-CH_3	*gem*-CH_2	POCH	POCCH	$\Delta^{POCH}_{obsd}/\Delta^{i}_{obsd}$[c,d]	$\Delta^{POCCH}_{obsd}/\Delta^{i}_{obsd}$[c,d]
17	292		508	490	157	$(CH_3)_c$, 1.67	0.55
18	312	112		495	140	$(CH_3)_c$, 1.59	0.44
						$(CH_3)_t$, 4.28	1.18
19a	322						
19b		108					

[a-d] The same as those in Table III.

TABLE V

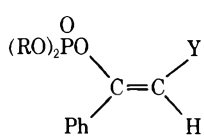
REVISED VINYL PHOSPHATE AND PHOSPHINATE SPECTRAL DATA[a]

		3-Vinyl H nmr				
			$\Delta = \delta_{Et_2O} -$			
Compd	Isomer ratio	$-\delta_{Et_2O}$	$\delta_{BF_3Et_2O}$	$-\delta_{CCl_4}$	$\Delta = \delta_{CCl_4} - \delta_{C_6D_6}$	$^4J_{POCCH}$, Hz
22						
H_B		5.28	−0.06	5.21	−0.36	2.2
H_C		5.05	−0.29	5.04	+0.07	2.0
(*Z*)-**1a**	65	6.42	−0.28	6.33	−0.15	1.0
(*E*)-**1b**	35	6.79	−0.02	6.69	+0.30	2.5
(*Z*)-**2a**	61–70	5.66	−0.16	5.60	+0.05	2.5
(*E*)-**2b**	30–39	5.79	−0.04	5.77	−0.23	2.8
(*Z*)-**3a**	60	6.31	−0.19	6.13	+0.21	2.3
(*E*)-**3b**	40	6.56	−0.08	6.45	−0.25	2.8
(*Z*)-**4a**	97	6.36	−0.21	6.14	+0.17	1.6
(*E*)-**4b**	3	6.59		6.49	−0.23	2.8

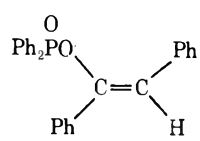
[a] Assignments are reversed from those reported previously in ref 2. The vinyl phosphates and **22** are synthesized from the reaction of triethyl phosphite (or ethyl diphenylphosphinite) with the appropriate α-bromo or chloro ketone (see ref 2 and Table VI).

This proton is now found to be cis to phenyl by a positive nuclear Overhauser effect (NOE) (63:37 of **3b**:**3a** changes to 47:53, a 16% *increase* in area for the vinyl proton of **3a**). The NOE was caused by irradiation at the ortho protons of the phenyl.[11] Thus the upfield proton belongs to the *Z* isomer **3a** and not to the *E* isomer **3b**, as previously believed.[2]

Previous attempts at observing an NOE from phosphorus or from methoxyl to the vinyl protons in either isomer of the *E*,*Z* mixture of dimethyl 1,2-diphenylvinyl phosphate (**20**) had failed.[2]



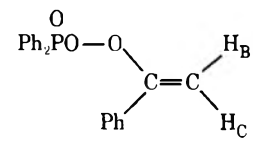
3a, R = C_2H_5; Y = Cl
(*Z*)-**20**, R = CH_3; Y = Ph



21

The mixture of *E*,*Z* stereoisomers **1a**,**b**, the one stereoisomer **1a** (from bromobenzyl phenyl ketone and triethyl phosphite), and the corresponding vinyl phosphinate **21** all have uv absorption at 283 nm which seemed to be more closely related to that of *cis*-stilbene (280 nm) than that of *trans*-stilbene (295 nm).[12] The minor isomer **1b** was separated (by preparative tlc) and was found to have uv absorption at 253 nm, confirming its new assignment as a *cis*-stilbene.

Table V gives data on two other methods previously used in correlating *E*,*Z* stereoisomerism[2] with the now revised structures for **1**–**4**. The β-vinyl protons trans to phosphate show small but significant shielding in benzene, compared to carbon tetrachloride, as expected.[2,13] Only **1** is anomolous. The boron trifluoride coordination of PO causes a greater deshielding of the trans-β-vinyl proton than the *cis*-β-vinyl proton, as observed for other vinyl phosphates and already discussed.[2] Thus these methods would seem to apply to most of the vinyl phosphates studied, including **2**–**4**.[14,15]



22

Revised Stereochemical Course of Perkow Reactions. —Table VI lists the isomer ratios of *gem*-phenyl vinyl phosphorylated species derived from the reaction of various α-haloketones with triethyl phosphite (**25**), dibutyl phenylphosphonite (**24**), and ethyl diphenyl phosphinite (**23**).[6,16] Consideration of this revised data together with other data is summarized as follows.

(*E*)-Vinyl phosphates predominate in the reactions of α-haloaldehydes[2,10] and α-chloroalkyl methyl ketones.[10] (*Z*)-Vinyl phosphates predominate in the Perkow reactions of α-bromoalkyl methyl ketones,[10] β-bromo-α-keto esters,[17] α-haloalkyl phenyl ketones

(11) Performed on a Varian XL-100 at 100 MHz by Professor J. F. Oth and staff, ETH, Zurich.

(12) H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," Wiley, New York, N. Y., 1962, pp 431–434.

(13) (a) F. Hruska, D. W. McBride, and T. Schaefer, *Can. J. Chem.*, **45**, 1081 (1967); (b) J. Ronague and D. H. Williams, *J. Chem. Soc.*, 2642 (1967); (c) A. Kemula and R. T. Iwamoto, *J. Phys. Chem.*, **72**, 2764 (1968); (d) M. Fetizon, J. Gore, P. Laszlo, and B. Waegell, *J. Org. Chem.*, **31**, 4047 (1966).

(14) The determination of $^3J_{^{13}CCH}$ coupling constants in (*E*)- and (*Z*)-vinyl phosphates is in progress by Dr. E. Pretsch, ETH, Zurich.

(15) The X-ray crystal structures of vinyl phosphinates related to **1a** and **4a** are being determined by Professor J. Van derVeen, Stevens Institute of Technology.

(16) R. K. Crouch, Ph.D. Thesis, Yeshiva University, 1972.

(17) (a) J. A. Stubbe and G. L. Kenyon, *Biochemistry*, **10**, 2669 (1971); (b) W. E. Bondinell and D. B. Sprinson, *Biochem. Biophys. Res. Commun.*, **40**, 1464 (1970).

TABLE VI

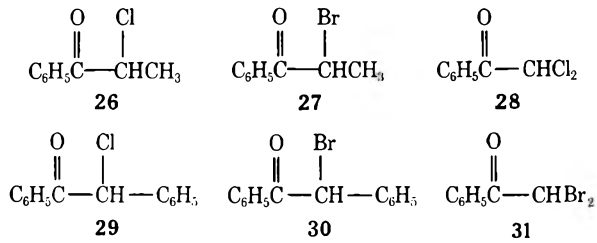
ISOMER RATIOS OF VINYL PHOSPHORYLATED SPECIES[a]

α-Halo ketone	Tricovalent phosphorus reagent	Isomer ratios[b] Z	E
26	23	40	60
	24	63	37
	25	61	39
27	23	50[c]	50[c]
	24	70[c]	30[c]
	25	70[c]	30[c]
28	23	18	82
	24	35	65
	25	60	40
29	23	100	0
	24	75	25
	25	65	35
30	23	100	0
	24	100	0
	25	100	0
31	23	100	0
	25	97	3

[a] Reaction conditions are given in ref 2, 3, and 6. [b] As determined by ^{1}H nmr on undistilled and distilled reaction mixtures. A change in isomer ratio upon distillation is noted only for the products **3a** and **3b** (from **28** and **25**). [c] Some ketophosphorylated product is formed in these reactions.[2]

such as **26** and **27**, and other halo and dihalo phenyl ketones (**28**–**31**). In the reactions of **24** and **23** with α-haloalkyl phenyl ketones (**26**–**28**) there is a tendency toward increased *E* isomeric vinyl phosphorylated products *vs.* reactions with **25**. Finally, **30** and **31** give only *Z* products with **23** or **24**.

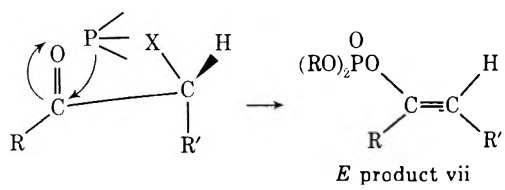
$(C_6H_5)_2POC_2H_5$ **23** $C_6H_5P(OC_4H_9)_2$ **24** $P(OC_2H_5)_3$ **25**



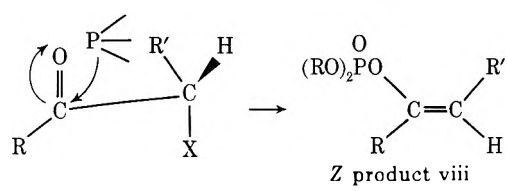
26 **27** **28**

29 **30** **31**

If we apply our previously postulated mechanism for the phosphite reactions,[3] *E* phosphates must result from the *irreversible* addition of phosphites to halogen eclipsed or halogen gauche conformers of α-halocarbonyl compounds while the *Z* phosphates are derived from halogen-staggered conformers.[18] While this concept of kinetically controlled carbonyl addition seems especially attractive for α-haloaldehydes which exist as the halogen eclipsed or gauche conformers in the ground state,[19] there are problems with the rationalization of some of the other cases.

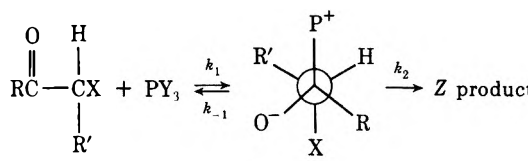


E product vii



Z product viii

An alternative explanation of the stereochemistry of the Perkow reaction involves the assumption of *reversible* phosphite addition to carbonyl and subsequent thermodynamic control in the elimination step leading to (*E*)- or (*Z*)-vinylphosphonium halides. The elimination is assumed to be anti, and the last step, Arbusov cleavage to the vinyl phosphorylated species, is assumed to be rapid, as already discussed.[3] For cases where the k_2 Cl/Br ratio $\geqq 1$,[3,6] this may mean that k_2 values are not much greater than k_{-1} or that the initial equilibrium for addition to carbonyl favors the α-chloro ketone while the elimination is faster for bromide loss, as usual.[20,21]



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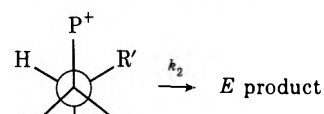


x

Thus the predominance of *E* products (vii, R = H) from α-haloaldehydes and *Z* products (viii) from α-halo ketones may reflect the greater thermodynamic stability of these products *vs.* their stereoisomers.[22]

The tendency toward equilibrium control is seen in comparing the k_2 Br/Cl ratios for the reactions of several α-halo ketones with the series triethyl phosphite (**25**), phosphonite **24**, and phosphinite **23**. Thus the ratios increase from 0.62 to 1.76 for *p*-nitrophenacyl halides and from 1.0 to 7.2 for 2-halocyclohexanones.[6] The predominance of *E* product in the diphenyl phosphinite reactions (as for **26** and **27**, Table VI) may reflect the greater stability of products with the bulky diphenylphosphinoxy group trans to the β-vinyl substituent.

Addition of a phosphinite to carbonyl should give a less stabilized intermediate (xi) than the corresponding phosphite adduct (xii) which can be stabilized by pentacovalency and other factors. Thus the carbonyl additions by phosphinites should tend to be more reversible than those of phosphites and therefore more subject to thermodynamic control.

The reactions of dibromo ketones or halobenzyl phenyl ketones (**29** and **30** in Table VI) with P(III) are not explicable by these arguments. Perkow re-

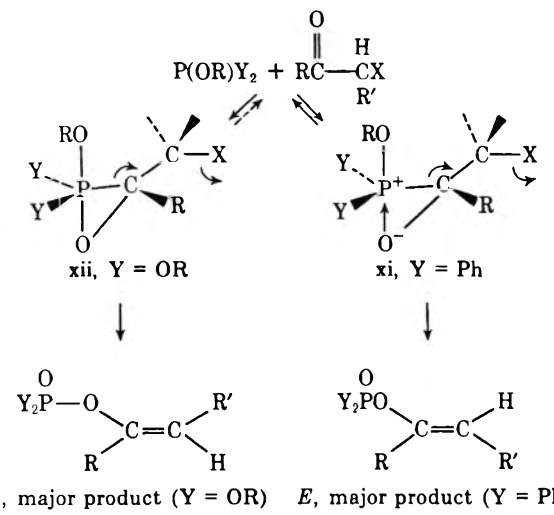
(18) See J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice Hall, Englewood Cliffs, N. J., 1971, Chapter 3, pp 84–116, for an excellent discussion of the stereochemistry of addition of nucleophiles to acyclic ketones and aldehydes.

(19) G. J. Karabatsos and D. J. Fenoglio, *J. Amer. Chem. Soc.*, **91**, 1124 (1969).

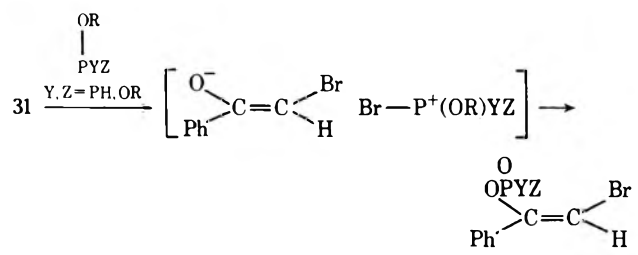
(20) The greater inductive effect of chlorine *vs.* bromine may suffice to explain a more favorable equilibrium for carbonyl addition.

(21) The postulate of rate-determining reversible carbonyl addition followed by stereochemistry-determining olefin formation is found in the Wittig reaction: A. J. Speziale and D. E. Bissing, *J. Amer. Chem. Soc.*, **85**, 3878 (1963).

(22) It is assumed that the "effective" size decreases $OPOPh_2$ > Ph > $OPO(OR)_2$, based on Dreiding models.



actions of α,α-dibromo ketones are characterized by exclusive formation of *Z* products, debromination in the presence of acetic acid,[6,23] and large k_2 Br/Cl ratios (~200) *vs.* those of the corresponding dichloroketone.[6] The data suggests that dibromo ketones react with P(III) *via* initial attack on bromine followed by O-phosphorylation of the resultant enolate halophosphonium ion pair. It is noteworthy that the (*Z*)-vinyl phosphate is the sole product formed in the phosphorylation of propiophenone or benzyl phenyl ketone under kinetic or equilibrium control conditions.[2]



The reactions of bromobenzyl phenyl ketone (**30**) with P(III), and possibly even of chlorobenzyl phenyl ketone (**29**) with phosphinites, may also proceed by halogen attack (at least in part). The k_2 Br/Cl ratios for these reactions range from 24 (triethyl phosphite reactions) to 205 (reactions with ethyl diphenylphosphinite),[6] and *Z* products predominate (Table VI).

In summary, Perkow reactions can occur *via* several mechanistic pathways. Evidence on the reversibility or nonreversibility of carbonyl addition in these reactions is needed.

Experimental Section[24]

The vinyl phosphates,[2,3] phosphonates,[2,6] and phosphinates[6,25] have been described. Eu(DPM)$_3$, mp 188–189°, and Pr(DPM)$_3$, mp 218–220°, were purchased from Alfa Inorganics.

General LIS Procedure.—The nmr spectrum of the vinyl phosphorylated species (1–2 × 10^{-4} mol) in dry CCl_4 (0.5 ml)–TMS was recorded at 60 MHz. Increments of lanthanide shift reagent were added and spectra recorded. From the slope of the plot of induced chemical shifts *vs.* the mole ratio of LIS reagent/substrate, the magnitude of induced shifts for certain protons in the substrate were calculated. All plots used to determine these shifts were linear over a range of LIS reagent/substrate of 0–0.4.

Registry No.—**1a**, 10409-52-6; **1b**, 10409-53-7; **2a**, 10409-50-4; **2b**, 10409-51-5; **3a**, 31327-17-0; **3b**, 31327-16-9; **4a**, 31428-82-7; **4b**, 31327-18-1; **5**, 31651-16-8; **6**, 38868-16-5; **7**, 38868-17-6; **8**, 38868-18-7; **9**, 38868-19-8; (*E*)-**10**, 31327-12-5; (*Z*)-**10**, 38858-37-6; **11a**, 31327-14-7; **11b**, 31327-15-8; (*E*)-**12**, 31327-13-6; (*Z*)-**12**, 38858-40-1; **13**, 5954-28-9; **14**, 31327-22-7; **15**, 1021-45-0; **16a**, 38858-41-2; **16b**, 38858-42-3; **17**, 30908-58-8; **18**, 10409-55-9; **19a**, 38778-62-0; **19b**, 38778-61-9; **20a**, 31327-10-3; **20b**, 31327-09-0; **22**, 31327-19-2; **23**, 719-80-2; **24**, 3030-90-8; **25**, 122-52-1; **26**, 6084-17-9; **27**, 2114-00-3; **28**, 2648-61-5; **29**, 447-31-4; **30**, 1484-50-0; **31**, 13665-04-8.

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(23) I. J. Borowitz, S. Firstenberg, E. W. R. Casper, and R. K. Crouch, *Phosphorus*, **1**, 301 (1972).

(24) Instrumental and relevant experimental techniques have been previously described.[2,25]

(25) I. J. Borowitz, K. C. Kirby, P. E. Rusek, and E. W. R. Casper, *J. Org. Chem.*, **36**, 88 (1971).

(26) I. J. Borowitz, E. W. R. Casper, R. K. Crouch, and K. C. Yee, *J. Org. Chem.*, **37**, 3873 (1972).

Proton Coupled Carbon-13 Magnetic Resonance Spectra. The Simple Amides

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The carbon-13 magnetic resonance spectra of a selection of simple amides are reported, with special emphasis placed upon the application of proton coupled spectra to the problem of peak assignment.

Because of their relationship to the biologically important polypeptide macromolecules, the amides have been the subject of numerous studies using diverse spectroscopic methods. As a result of this intensive study, a great deal is known regarding the molecular and electronic structure of these molecules.[1] Thus, the amides are essentially planar, with the nitrogen–acyl bond restricted to two rotameric states which are separated by an energy barrier of about 20 kcal/mol. Proton magnetic resonance spectroscopy has been extensively used to study these conformations and their interconversions.

The amides have also received the attention of carbon-13 magnetic resonance (^{13}C nmr) spectroscopists. Using double resonance techniques, it has been shown that *N*-methyl carbons which are syn[2] to the carbonyl oxygen in *N*,*N*-dimethylamides are shielded relative to the anti by 3–5 ppm.[3] A more recent publication[4] has concentrated largely upon the relaxation times of the carbons of simple amides, and it is clear that T_1 measurements will be a useful aid in distinguishing the syn and anti α-carbon resonances of such molecules as *N*,*N*-dibutylformamide.

As part of a more extended investigation of ^{13}C nmr spectra of polypeptides,[5] we have undertaken a brief survey of the amides. The major thrust of our study has been to develop additional methods by which the carbon resonances of more complex molecules may be assigned. Our prior experiences with the esters[6] suggested that carbon–proton coupling might be useful in this regard. The present paper describes our progress in the measurement of proton coupled ^{13}C nmr spectra of amides.

Experimental Section

All compounds were commercially available and were used without purification. *N*-Deuterioamides were prepared by treatment with deuterium oxide or methanol-d_1 followed by distillation.

Carbon-13 nuclear magnetic resonance spectra were measured on a Varian XL-100 spectrometer modified for Fourier transform spectroscopy in a manner which has been previously described.[7] Carbon chemical shifts were measured in aqueous solutions (10% v/v) relative to internal (2–5%) 1,4-dioxane. The chemical shifts so measured were than related to external carbon disulfide on the basis of the chemical shift of 1,4-dioxane measured relative to that standard (126.2 ppm). Proton coupled ^{13}C nmr spectra were measured using neat solutions when possible. For crystalline amides, proton coupled spectra were measured in aqueous solutions.

For the preliminary coherent decoupling experiments reported in this paper, decoupling power was adjusted to the minimum necessary for complete decoupling. On our basic Varian XL-100 spectrometer,[7] this generally corresponded to about 110 dB on the low power range.

Results and Discussion

Carbon Chemical Shifts.—Carbon chemical shifts reported in this paper are presented in Tables I and II. To facilitate later comparison of these spectra to those of peptides and amino acid derivatives,[5] aqueous solutions were used in all measurements. In many cases, peak assignments were derived from the literature.[3,4] These assignments were confirmed and extended using carbon–proton coupling constants measured in this study (*vide infra*).

TABLE I

CARBON CHEMICAL SHIFTS[a] IN SIMPLE AMIDES

Registry no.	Amide	C=O	—NCH$_2$— anti	—NCH$_2$— syn	CCH$_3$
75-12-7	Formamide	26.1			
123-39-7	*N*-Methylformamide (trans)	28.2		168.3	
	(cis)[b]	25.0	164.7		
68-12-2	*N*,*N*-Dimethylformamide	28.1	155.9	161.4	
60-35-5	Acetamide	15.6			171.4
79-16-3	*N*-Methylacetamide	18.3		166.8	171.0
127-19-5	*N*,*N*-Dimethylacetamide	19.0	154.6	157.5	172.2

[a] Measured relative to external carbon disulfide. [b] Spectrum measured as a 25% aqueous solution.

TABLE II

CARBON CHEMICAL SHIFTS[a] OF FORMYL- AND ACETYLSARCOSINES

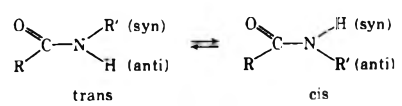
Registry no.	Sarcosine	COOH	NCH$_2$	NCH$_3$	O ‖ –CN	CH$_3$C
38456-66-5	*N*-Formylsarcosine (trans)	20.5	146.5	157.0	27.3	
	(cis)	19.4	141.5	161.9	26.7	
5888-91-5	*N*-Acetylsarcosine (trans)	19.4	143.1	155.3	18.0	172.2
	(cis)	19.5	140.4	158.0	17.9	172.4

[a] All chemical shifts measured relative to carbon disulfide.

The most significant source of carbon chemical shift differences in amides is that due to the carbonyl group. *N*-Methyl carbons which are syn to the carbonyl oxygen are invariably shielded relative to the anti case. There appears to be some question regarding the source

(1) M. B. Robin, F. A. Bovey, and H. Basch in "The Chemistry of Amides," J. Zabicky, Ed., Interscience, New York, N. Y., 1970, Chapter 1.

(2) Throughout the subsequent discussion syn will be used to describe groups which are on the same side of the amide linkage as the carbonyl oxygen. The term anti will denote the opposite geometry. Such a convention will leave the terms cis and trans to describe the two stable conformers around the amide function.



trans cis

(3) W. McFarlane, *Chem. Commun.*, 418 (1970).

(4) G. C. Levy and G. L. Nelson, *J. Amer. Chem. Soc.*, **94**, 4897 (1972).

(5) D. E. Dorman and F. A. Bovey, in preparation.

(6) D. R. Bauer, D. E. Dorman, and J. D. Roberts, in preparation.

(7) H. Sternlicht and D. M. Zuckerman, *Rev. Sci. Instrum.*, **43**, 525 (1972).

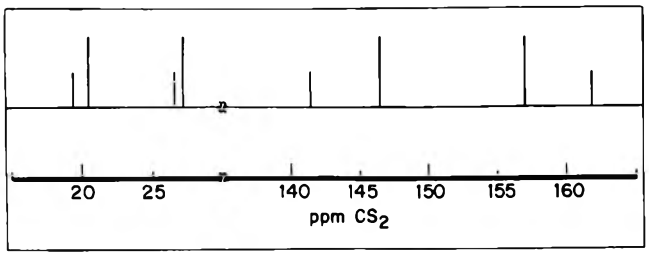
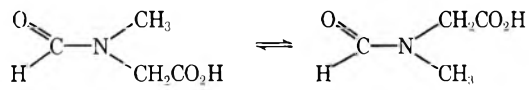


Figure 1.—Schematic representation of the ^{13}C nmr spectrum of *N*-formylsarcosine. The more intense set of peaks represents the spectrum of the major or trans conformer. The back-to-back pattern shown in the upfield resonances is typical of the spectra of sarcosine derivatives.

of this shielding proximity effect. McFarlane,[3] citing evidence derived from proton chemical shifts and one-bond carbon–proton coupling,[8] attributed it to the electric field associated with the carbon–oxygen bond. More recently[4] the proximity effect of the carbonyl oxygen has been discussed in terms of steric compression. Whatever the source of this effect, it is thought to extend its influence even to the terminal methyl carbons of *N*,*N*-di-*n*-butylformamide.[4]

The existence of such an effect may have important implications in the ^{13}C nmr study of the conformations of peptides. An indication of this is apparent in the spectra of *N*-acylsarcosines (Table II). Even in the absence of any data other than the carbon chemical shifts of these compounds, full and reliable peak assignments may be made. The case of *N*-formylsarcosine will be used as an example. The aqueous solution of this compound shows the presence of the two unequally populated conformers, cis and trans. Within



cis trans

the spectra of each of these conformers the two upfield resonances may be differentiated by off-resonance decoupling.[9] On the basis of the shielding effect of the carbonyl group we would predict that (1) the *N*-methyl resonance of the cis conformer would be upfield relative to the trans; and (2) the *N*-methylene resonance of the trans conformer would be the more shielded. This should lead to a back-to-back pattern in the upfield carbon resonances, as has been observed for similar compounds using proton magnetic resonance spectroscopy.[10] This is indeed observed in the ^{13}C nmr spectrum of this compound, as is schematically shown in Figure 1. Similar methods of assignment have proven useful in the ^{13}C nmr spectra of proline derivatives.[5]

Proton Coupled ^{13}C Nmr Spectra.—A previous study[6] of the proton coupled ^{13}C nmr spectra of ethers and esters demonstrated that geminal and vicinal carbon–proton coupling constants could be easily measured in simple compounds. Such data were found to be useful in the conformational analysis of these systems. Corresponding measurements on amides should be useful in making peak assignments. Unfortunately, the spectra of amides are subject to problems not present in the earlier investigation.[6] The presence of the ^{14}N nucleus in amides, for example, might be expected to lead to additional complexities in their spectra. The presence in many amides of an exchangeable N proton is another potential complication. Because virtually every carbon nucleus in these simple amides is spin coupled to the N proton, any exchange phenomena could lead to irreproducible results. This problem can be avoided by exchanging the N protons with deuterium, a device which also leads to simplification of the proton coupled spectra.

It is largely due to problems of this nature that the coupling constant data of Tables III and IV must be considered approximate. Even in view of these limitations, however, the present data are sufficient to provide important information for peak assignments and conformational analysis. Thus, as shown in Figure 2, the coupling between the *N*-methyl carbon and formyl proton nuclei of *N*-methylformamide is strongly dependent upon the dihedral angle about the nitrogen–acyl bond. In the trans isomer, wherein the dihedral angle between the two coupled nuclei is 180°, this vicinal carbon–proton coupling constant is about 5 Hz. For the cis conformer, corresponding to a dihedral angle of 0°, the coupling is too small to be resolved under the conditions of the experiment. Clearly such differences

TABLE III

COUPLING[a] INVOLVING THE CARBONYL CARBON

Amide	$^1J_{CH}$	$^2J_{CCH}$	$^2J_{CNH}$	$^3J_{CNCH}$
Formamide	192.8		2.4, *ca.* 5.5	
N-Methylformamide-d_1				
(trans)	191.5			3.1
(cis)	189.1			*ca.* 4.3
N-Methylformamide				
(trans)	191.7		*ca.* 3.7	*ca.* 3.7
(cis)	189.1		*b*	*b*
Acetamide[c]		5.9	2.65, 2.65	
N-Methylacetamide-d_1		6.1		3.5
N-Methylacetamide		5.9	3.7	3.7

[a] All coupling constants are in hertz, and are accurate within ±0.2 Hz. [b] Not resolved. [c] Measured in saturated aqueous solution.

TABLE IV

COUPLING[a] INVOLVING *N*-METHYL CARBONS

Amide	$^1J_{CH}$	$^2J_{CNH}$	$^3J_{CNCH}$
N-Methylformamide-d_1			
(cis)			*b*
(trans)			5.1
N-Methylformamide			
(cis)	137.3	*b*	*b*
(trans)	137.9	2.8	4.8
N,*N*-Dimethylformamide			
(syn) CH_3	138.5		*ca.* 3.4,[c] *ca.* 3.4[d]
(anti) CH_3	138.9		*ca.* 3.4,[c] *ca.* 2.0[d]
N-Methylacetamide	138.2	2.7	

[a] All coupling constants are reported in hertz, and are accurate to approximately ±0.2 Hz. [b] Not resolved. [c] Vicinal coupling between the carbon of one methyl group and the protons of the other. [d] Vicinal coupling between *N*-methyl carbons and the formyl proton.

(8) W. T. Raynes and T. A. Sutherley, *Mol. Phys.*, **18**, 129 (1970); **17**, 547 (1969).

(9) H. J. Reich, M. Jautelat, M. T. Messe, F. J. Weigert, and J. D. Roberts, *J. Amer. Chem. Soc.*, **91**, 7445 (1969).

(10) F. A. Bovey, J. J. Ryan, and F. P. Hood, *Macromolecules*, **1**, 305 (1968).

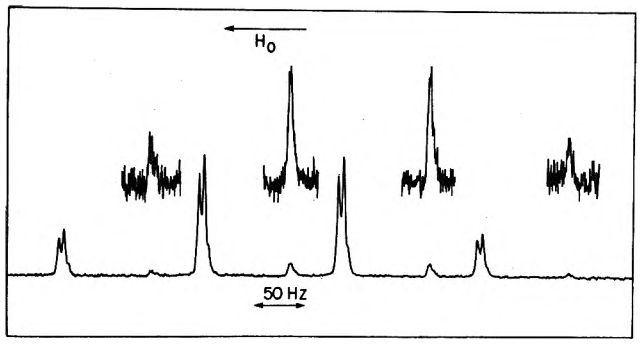


Figure 2.—The proton coupled spectrum of the *N*-methyl carbons of *N*-methylformamide. Minor peaks, which are shown at higher gain in the insets, are those of the minor cis conformer.

in coupling are of potential use in peak assignment and conformational analysis in these systems.

A more striking dihedral dependence is shown by acetamide (*cf.* Figure 3). Here, the methyl carbon is coupled observably to only one of the N protons ($^3J_{CCNH}$ = 7.1 Hz). In the spectrum of *N*-methylacetamide, the acetyl methyl carbon resonance is coupled to none but the directly attached protons. Because this latter compound is known to be 100% trans,[11] these results indicate that the methyl carbon of acetamide is coupled only to the syn N proton.

One-bond carbon–proton coupling constants also have occasional application to the problem of peak assignment. In the spectrum of *N*-methylacetamide, for example, the two methyl resonances differ by less than 5 ppm, a surprisingly small difference. The indicated assigment (Table I) can be supported, however, by the proton coupled ^{13}C nmr spectrum. In the latter spectrum the one-bond carbon–proton coupling constant for the high-field methyl resonance is found to be approximately 128 Hz, while that of the low-field methyl quartet is about 138 Hz. The same coupling constants can be conveniently measured from the ^{13}C side bands of the proton spectrum, in which there is no question of assignment.[11] Using this method, the low-field methyl carbon resonance can be related to the *N*-methyl proton resonance, thereby confirming the above assignment.

In the spectrum of *N*-acetylsarcosine, the chemical shifts of the carbonyl nuclei were found to be rather similar (*cf.* Table II). By correlation with the spectrum of *N*-formylsarcosine, the peaks near 19.5 ppm were assigned to the carboxyl resonance. Confirmation of this assignment was derived from the proton coupled ^{13}C nmr spectrum. The acetyl carbonyl carbon of *N*-acetylsarcosine would be expected to be coupled to the protons of both methyl groups and the *N*-methylene group, as well as to the ^{14}N nucleus. The carboxyl carbon, however, would be coupled only to the adjacent methylene protons. In the proton coupled ^{13}C nmr spectrum, the resonances near 19.5 ppm appeared as triplets ($^2J_{CCH} \cong 5.7$ Hz), thereby confirming their assignment to the carboxyl carbons.

These results, taken in conjunction with the data in Tables III and IV, indicate that proton coupled ^{13}C nmr spectra may provide important information regarding the peak assignment and conformational analysis in such systems. More recent results indicate that proper control of the temperature at which the spectra are taken leads to much narrower lines and thus more precise coupling data. Continuing experiments designed to investigate these effects, and to evaluate the application of carbon–proton coupling constants to problems in conformational analysis, are in progress.

(11) L. A. LaPlanche and M. T. Rogers, *J. Amer. Chem. Soc.*, **86**, 337 (1964).

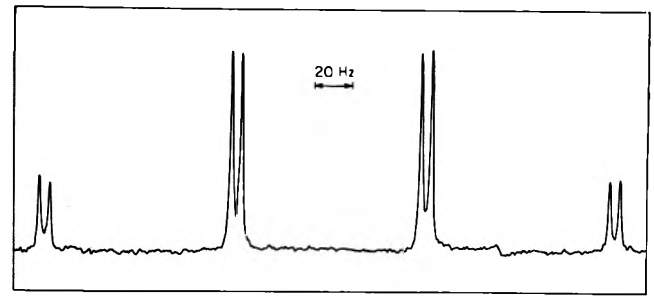


Figure 3.—The proton coupled methyl resonance of acetamide. Each portion of the widely split quartet shows evidence of vicinal coupling to only one N proton.

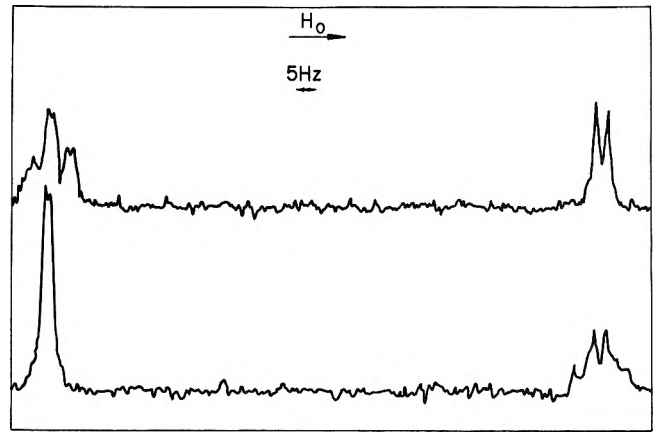


Figure 4.—Coherent proton decoupling experiments with *N*,*N*-dimethylformamide. In the upper trace, the decoupling frequency has been set on the upfield *N*-methyl proton resonance. The upfield carbon resonance shows residual vicinal coupling to the formyl proton. The lower trace was obtained when the decoupling frequency was moved to the lower *N*-methyl proton resonance.

Coherent Proton Decoupling.—In many amides, it may be desirable to measure a particular coupling constant in the absence of any other carbon–proton coupling. As an example of such a situation, we may consider the case of *N*,*N*-dimethylformamide. Through measurements of the coupling between the *N*-methyl carbons and the formyl proton, one can detect dihedral angle effects in such systems. Unfortunately, each of the methyl carbons in *N*,*N*-dimethylformamide is also coupled to six methyl protons, and the resonances of these spectra are accordingly complex.

It is possible in this system, however, to decouple the *N*-methyl proton resonances without significant perturbation of the formyl proton resonance (*cf.* Figure 4). Under such conditions the residual coupling is easily estimated. As observed for the simpler cases, the coupling constant for the syn *N*-methyl carbon was larger (3.4 Hz) than that of the anti ($\leq$2.0 Hz). It is similarly possible to decouple only the formyl proton, thus facilitating the measurement of the coupling between each methyl carbon and the protons of the other methyl group. This vicinal coupling was approxi-

mately the same (3.4 Hz) for each methyl carbon. Similar techniques may find application in the analysis of the conformations of *N*-formyl derivatives of greater complexity.

Conclusion

One of the most important carbon-13 chemical shift effects seen in the amides is a proximity effect associated with the carbonyl oxygen. Thus, *N*-alkyl carbons which are syn to this oxygen are strongly shielded. While at present this effect has only been recognized for carbon nuclei attached to the nitrogen of amides or the ether oxygen of esters,[6] there appears to be no reason why a similar effect cannot occur at the β carbon of amino acids. Such an effect could have important application to the conformational analysis of such systems.

Carbon–proton coupling appears to hold promise of useful applications in the conformational analysis and peak assignment for at least the simple amides, and may be useful in further investigations into the shielding effect of the carbonyl group in small molecules. Such experiments are currently in progress.

Carolenin and Carolenalin, Two New Guaianolides in *Helenium autumnale* L. from North Carolina[1,2]

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The major sesquiterpene lactones found in *Helenium autumnale* L. collected during the summer in North Carolina were not the pseudoguaianolide helenalin or the norsesquiterpene lactone, dihydromexicanin E, but were the new guaianolides, carolenin and carolenalin. The structures of carolenalin and carolenin have been shown to be **1** and **13** on the basis of chemical transformations and spectral evidence.

The constituents of *Helenium autumnale* L. collected from different populations were previously examined and reported to contain helenalin,[7-10] dihydromexicanin E,[11-12] helenium lactone,[13] 2-acetyl flexuosin A,[14] autumnolide,[14] tenulin,[15] mexicanin I,[15] and flexuosin A.[15] In the course of a search for convenient supply of the pseudoguaianolide helenalin for investigation of the relationship between the sesquiterpene lactone structure and the antitumor or cytotoxic activity,[16-19] we had occasion to extract a batch of *Helenium autumnale* L., collected during the summer in the vicinity of Durham, N. C. We report herein the isolation and structural elucidation of two new guaianolides, carolenalin and carolenin.[20]

Carolenalin and carolenin, isolated from a chloroform extract of the finely ground plant material by fractionation involving successive solvent partitions and silica gel chromatography, were assigned structure **1** and **13**, respectively, on the basis of the following chemical transformations and spectral evidence.

Carolenalin (**1**) was isolated as an oil in 0.4% yield and had infrared bands at 3500, 1760, and 1640 cm^{-1}, thus indicating the presence of a hydroxyl group, a γ-lactone carbonyl, and a carbon–carbon double bond. The nmr spectrum of carolenalin (Table I) is in accord with the structure **1**. The vinyl methyl protons at C-10 appeared as a broad singlet at δ 1.75 and the methyl groups at C-11 and C-4 were seen, respectively, as a doublet (J = 7.5 Hz) at 1.19 and a sharp singlet at 1.08. Other nmr signals were seen at δ 5.35 (1 H, m, H-9), 5.09 (1 H, m, H-8), and 3.74 (1 H, t, J = 3.0 Hz, H-3) which was shifted downfield to 4.79 (q, J = 3.0, 5.25 Hz) in the monoacetate **2** and 5.45 (t, J = 3.0 Hz) in the diacetate **3** as described below.

Acetylation of **1** with acetic anhydride in pyridine for 3 days at room temperature yielded approximately equal amounts of a monoacetate **2** (mp 160–161°, $C_{17}H_{24}O_5$) and a diacetate **3** (mp 146–148°, $C_{19}H_{26}O_6$),[21] indicating the presence of two hydroxyl groups. Mass spectral peaks at *m/e* 308 (M^+), 290 (M − 18) (M − H_2O), 248 (M − 60) (M − AcOH), and 230 (M − 78) (M − H_2O and AcOH), and ir absorption at 3580 (OH) and 1740 cm^{-1} (acetyl C=O) showed that **2** was a

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(2) Presented in part at the 13th Annual Meeting of the American Society of Pharmacognosy, The Ohio State University, Columbus, Ohio, July 21, 1972.

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(6) Medicinal Chemistry Trainee; supported by Public Health Training Grant 5T01-AM01770-03 from the National Institute of General Medical Sciences, National Institutes of Health.

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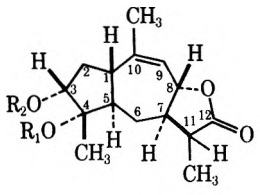
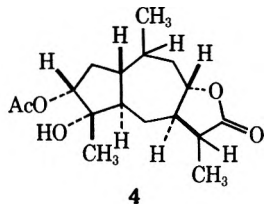
(20) The plant material used in the present work contained neither helenalin nor dihydromexicanin E, although the latter compound was isolated before from the same plant species in almost the same season and at the same site.[11]

(21) The formation of a diacetate (**3**) with acetic anhydride–pyridine suggested that a vicinal diol moiety was present, since under this mild reaction condition **3** could only be formed *via* a neighboring group participation mechanism.

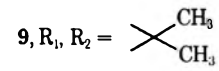
hydroxy monoacetate. That the remaining hydroxyl group in **2** was tertiary was evidenced by the fact that **2** showed a sharp D_2O-exchangeable one-proton singlet at δ 4.42 in the nmr spectrum (DMSO-d_6). The structure of **2** and **3** was also verified by the appearance of the three-proton singlet for the acetyl methyl groups in **2** and **3** at δ 2.10 and 2.00 and 2.03, respectively.



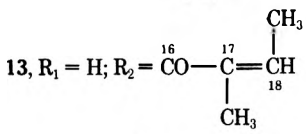
1, $R_1 = R_2 = H$
2, $R_1 = H$; $R_2 = Ac$
3, $R_1 = R_2 = Ac$



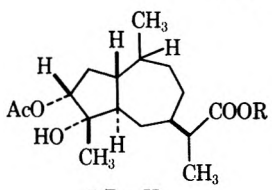
4



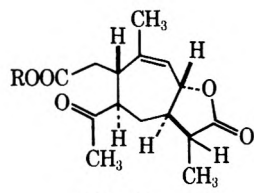
9, $R_1, R_2 =$



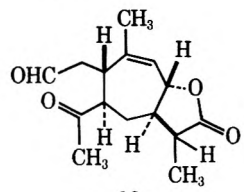
13, $R_1 = H$; $R_2 =$



5, R = H
6, R = CH_3



7, R = H
8, R = CH_3



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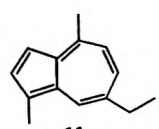


11

Catalytic hydrogenation of **2** with platinum oxide in ethyl acetate afforded a mixture of the corresponding dihydro compound **4** (mp 221–222°, $C_{17}H_{26}O_5$) whose nmr spectrum showed a new secondary methyl group at C-10 as a doublet (J = 6.0 Hz) at δ 0.95, and an acid **5** (mp 125–126°, $C_{17}H_{28}O_5$) whose nmr spectrum showed the disappearance of the characteristic lactonic (H-8) and vinylic (H-9) protons in the low-field region. Methylation of **5** with diazomethane gave a methyl ester (**6**, oil) which showed a carboxymethyl singlet at δ 3.63. The ready formation of the acid **5** by hydrogenolysis indicated an allylic disposition for the oxygen atom of the lactone ring. Support for this suggestion was found in the nature of the signal for the lactonic proton at H-8 in the nmr spectra of **2** and **4**. The H-8 proton in **4** (4.53, 1 H, m) is upfield shifted compared to the H-8 signal in **2** (5.08, 1 H, m).

Oxidation of **1** with Jones reagent at room temperature furnished a keto acid **7** (mp 171–172°, $C_{12}H_{20}O_5$). The nmr spectrum of **7** exhibited, instead of a tertiary methyl singlet at δ 1.08 (C-4 CH_3) as seen in **1**, a new sharp three-proton singlet at 2.14 attributable to the methyl ketone. Methylation of **7** yielded the corresponding ester **8**. The facile reaction of **1** to form acetonide (**9**) from acetone and *p*-toluenesulfonic acid, and

TABLE I
NMR SPECTRAL DATA FOR CAROLENALIN, CAROLENIN, AND DERIVATIVES[a]

Compd	H-3	H-8	H-9	C-11 CH_3	C-10 CH_3	C-4 CH_3	Ac	Misc
1	3.74	5.09	5.35	1.19	1.75	1.08		
	t (3.0)	m	m	d (7.5)	m	s		
2	4.79	5.08	5.35	1.19	1.75	1.13	2.10	
	dd (3.0, 5.25)	m	m	d (7.5)	m	s	s	
3	5.45[b]	5.15	5.45	1.22	1.78	1.32	2.00	
	t (3.0)	m	m	d (7.5)	m	s	s	
							2.03	
							s	
4	4.80	4.53		1.15	0.95	1.22	2.08	
	dd (6.0, 9.75)	m		d (7.5)	d (6.0)	s	s	
5	4.78			1.14	0.89	1.19	2.10	
	dd (4.5, 7.5)			d (7.5)	d (6.0)	s	s	
6	4.80			1.11	0.88	1.18	2.08	3.63[c]
	dd (5.25, 7.5)			d (7.5)	d (6.0)	s	s	s
7		5.42	5.20	1.20	1.82	2.14		
		m	m	d (6.75)	m	s		
8		5.45	5.25	1.20	1.82	2.14		3.67[c]
		m	m	d (6.75)	m	s		s
9	4.20	5.40	5.15	1.18	1.78	1.45		1.38[d]
	dd (1.5, 6.0)	m	m	d (6.75)	m	s		s
10		5.49	5.25	1.20	1.80	2.15		9.84[e]
		m	m	d (6.75)	m	s		
13	4.88	5.14	5.40	1.22	1.78	1.18		6.18[f]
	dd (3.0, 4.5)	m	m	d (6.75)	m	s		m
								1.92[g]
								s

[a] These spectra were measured in $CDCl_3$ with a Jeolco C-60 HL nmr spectrometer using TMS as an internal standard. All chemical shifts were reported in δ (ppm) values and the coupling constants (figures in parentheses) in hertz. Signals are characterized in the usual way: s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. H-3, H-8, and H-9 each integrated for one proton. Methyl as well as acetyl signals had three proton intensities. [b] Overlapped with H-9. [c] Carboxymethyl group. [d] Geminal dimethyl groups (6 H) of the acetonide. [e] Aldehyde (1 H). [f] H-18. [g] C-17 and C-18 methyl groups (6 H).

aldehyde[22] [**10**, nmr δ 9.84 (aldehyde) and 2.15 (methyl ketone)] by treatment with sodium periodate, indicated the presence of the partial structure $-CH(OH)C(OH)-(CH_3)-$ in carolenalin. Dehydrogenation of **1** with 30% palladium on carbon led to the expected chamazulene (**11**), which was characterized as the trinitrobenzene adduct (mp 128–129°, $C_{14}H_{16}\cdot C_6H_3O_6N_3$) and was shown to be identical with an authentic sample of chamazulene trinitrobenzene adduct[23] by mixture melting point determination and direct infrared spectral comparison.

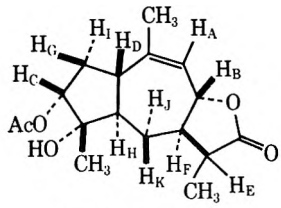
Added confirmation for the assignment of structure **1** to carolenalin was obtained by detailed double resonance experiments of monoacetate **2**. When the C-8 lactonic proton (H_B) at 515 Hz was irradiated, the vinyl proton at C-9 (H_A) collapsed to a broad singlet. Irradiation of the C-1 proton (H_D) at 322 Hz caused the signal for the lactonic proton (multiplet) at C-8 (H_B) to collapse to a quartet with J_{AB} = 4.0 and J_{BF} = 7.2 Hz. The coupling constant of the protons at C-7 and C-8 ($J_{7,8}$ = 7.2 Hz) suggested the trans-fused lactone ring. Dreiding models of this compound indicate the feasibility of this suggestion, since the conformation of the seven-membered ring is very rigid. Additional spin-decoupling studies are summarized in Table II.

The conformation of carolenalin monoacetate (**12**) was determined by nuclear Overhauser effect (NOE)

(22) The attempted purification of this compound was unsuccessful.

(23) The authors are indebted to Dr. Ken-ichi Takeda, Shionogi Research Lab, Osaka, Japan, for a generous sample of chamazulene trinitrobenzene adduct.

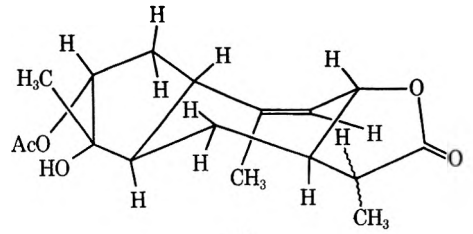
TABLE II
DOUBLE-RESONANCE (100 MHz) NMR DATA FOR CAROLENALIN MONOACETATE[a]



Original proton signal	Position of irradiation, Hz	Signal change after irradiation
H_A m	265 (H_E, H_F)	dd (2.3, 4.0)
	322 (H_D)	d (4.0)
	515 (H_B)	s (broad)
H_B m	265 (H_E, H_F)	dd (4.0, 1.8)
	322 (H_D)	dd (7.2, 4.0)
H_C dd (2.8, 5.0)	220 (H_G, H_I)	s
H_D m	210 ($H_{H,G,I}$)	s (broad)

[a] The double-resonance studies were done on a Varian HA-100 nmr spectrometer in $CDCl_3$ and the values differ slightly from those recorded in Table I, which were obtained from 60-MHz studies.

studies. Irradiation of the C-4 methyl signal at 113 Hz increased the intensity of the H-3 to 12%, suggesting that the C-4 methyl and the H-3 are cis to each other.



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Irradiation of the H-1 proton at 320 Hz also produced a positive response (11% increase) on the H-8 proton signal, indicating a 1,4-diaxial relationship between these two protons. Thus, if the C_8 H configuration is β, as is likely, the C_1 H configuration is then β. Since the biogenetic evidence indicates that the naturally occurring guaianolide-type sesquiterpene lactones isolated so far all possess a β-oriented C-4 methyl group and an α-oriented C-7 proton, this consideration, coupled with the above observations, leads to the conclusion that the stereochemistry of carolenalin is as depicted in structure **1** (or **12**) in which the configuration of the C-11 methyl group remains to be determined. The configuration of C_5 H is assigned α since an alternative is not supported by models on the basis of a 1,4-diaxial relationship between H-1 and H-8.

The other new guaianolide carolenin (**13**) was also isolated as an oil. Carolenin showed a molecular ion peak at *m/e* 348 and a prominent peak at *m/e* 330 (M − 18) in the mass spectrum. The presence of an α,β-unsaturated ester group was revealed by an ir band at 1713 cm^{-1}, and by a characteristic ion of *m/e* 83 (base peak) [$COC(CH_3)=CH(CH_3)$] (*i.e.*, the cleavage of esters of angelic, tiglic, and senecioic acids).[24] That carolenin (**13**) is probably an angelate ester of carolenalin (**1**) was indicated by the nmr spectrum, in which the vinyl proton at C-18 of the ester moiety appeared as a one-proton multiplet at δ 6.10, a value which is characteristic of an angeloyl residue.[23,25] The two vinyl methyl groups (C-17 and C-18) appeared as one sharp singlet at δ 1.92 (6 H). Other nmr signals of **13** (Table I) are nearly identical in form and multiplicity with the signals for the corresponding groups of carolenalin (**1**). The downfield shift of the proton at C-3 (4.88, q, J = 3.0, 4.5 Hz) in **13** compared with that in the nmr spectrum of **1**, in which the H-3 signal appeared at δ 3.73 (t, J = 3.0 Hz), further indicated that this angeloyl side chain is located at the C-3 position. To further confirm the structure of carolenin, it was hydrolyzed with potassium hydroxide in methanol, with the formation of carolenalin (**1**) (identified with an authentic sample by ir comparison), a C-11 epimer of carolenalin,[26] and an angelic acid which was isolated as *p*-phenylphenacyl ester and was shown to be identical with an authentic sample of *p*-phenylphenacyl angelate by mixture melting point determination. The foregoing evidence leads to the assignment of structure **13** for carolenin beyond doubt.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and were corrected. Unless otherwise specified, optical rotations were determined on a Perkin-Elmer 141 polarimeter. Ultraviolet (uv) spectra were determined on a Cary Model 15 spectrophotometer. Infrared (ir) spectra were measured in chloroform with a Perkin-Elmer 257 grating infrared spectrophotometer. Mass spectra were determined on an A. E. I. MS-902 instrument at 70 eV using a direct inlet system. We thank Mr. F. Williams of the Research Triangle Center for Mass Spectrometry for these determinations. Silica gel and neutral alumina for column chromatography refers to Baker A. R. No. 3405 and Bio-Rad neutral alumina AG-7 (100–200 mesh), respectively; and silica gel for thin layer chromatography (tlc) refers to Merck silica gel G developed with chloroform–acetone (3:1) and visualized by spraying with concentrated sulfuric acid and heating. Silica gel for preparative tlc refers to Merck silica gel GF-254. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Ga.

Isolation of Carolenin (13) and Carolenalin (1).—The *Helenium autumnale* L. (*Compositae*) used was from a collection made on July 26, 1971, along the meadow approximately 0.4 mile south of Tar River station and east of US 15 in Granvilk County, N. C.[27] The ground, air-dried, whole plant material (40 lb) was exhaustively extracted with chloroform and worked up in the usual manner.[28] This gave 359 g of a dark-brown syrup. Tlc showed that this crude extract was a mixture of two major components. This extract was then dissolved in a minimum amount of benzene and chromatographed over 1.5 kg of silica gel, using benzene, ethyl acetate, and ethyl acetate–methanol as eluents. The first 3.5 l. of benzene (fractions 1–7) eluted minor quantities of nonpolar substances. The subsequent 10 l. of benzene eluate (fractions 8–28) afforded a mixture of the above-mentioned two components (carolenin and carolenalin). The polar fractions 29–35

(24) T. A. Geissman and T. S. Griffin, *Rev. Latinoamer. Quim.*, **2**, 81 (1971), and references cited therein.

(25) (a) It should be noted that the formation of the tiglate is due to the isomerization of the angelate during the alkaline hydrolytic procedure. We assigned the vinyl proton signal of carolenin to an angelate instead of a tiglate because the observed characteristic chemical shift of the former (δ 6.18) is comparable with those of the angeloyl esters of tomentosin,[24] eriofertin,[25b] and fastigilin A[25c] in the nmr spectra. (b) T. Saitoh, T. A. Geissman, T. G. Waddell, W. Herz, and S. V. Bhat, *Rev. Latinoamer. Quim.*, **2**, 69 (1971), and references cited therein. (c) W. Herz, S. Rajappa, S. K. Roy, J. J. Schmid, and R. N. Mirrington, *Tetrahedron*, **22**, 1907 (1966).

(26) The cooccurrence of carolenalin and carolenin, coupled with the fact that this epimeric compound was only isolated in small quantity, led to the conclusion that carolenin is the angelate ester of carolenalin and not of the C-11 epimer of carolenalin.

(27) The authors wish to thank Mr. S. W. Leonard, Department of Botany, University of North Carolina at Chapel Hill, for collecting and identifying the plant material. A Voucher specimen has been placed in the herbarium of the Botany Department, UNC-CH.

(28) K. H. Lee, S. Matsueda, and T. A. Geissman, *Physochemistry*, **10**, 405 (1971).

(ethyl acetate, 3 l.) and 36–40 (ethyl acetate–methanol, 6:1, 2 l.) yielded a mixture of mainly carolenalin and very small amounts of more polar substances whose structures are now under investigation.

The brown syrup obtained from fractions 8–28 (192 g) was rechromatographed on silica gel (1 kg). Elution with benzene (19.5 l.) gave 71.8 g of brown oil (crude carolenin). The tlc analysis of this oil showed only a faster moving single spot. One rechromatography of this oil (20 g) on silica gel (200 g) using benzene and benzene–chloroform as eluents afforded the pure carolenin (0.97 g)[29] (**13**): $[\alpha]^{25}D$ – 101.9° (*c* 0.598, MeOH); ir bands at 3586 (hydroxyl), 1765 (γ-lactone), 1713 (α,β-unsaturated ester carbonyl), and 1643 cm^{-1} (unsaturation); nmr data listed in Table I.

The materials remaining in the column after the removal of carolenin were further eluted with chloroform (6 l.) to yield carolenalin (**1**)[29] as a brown, viscous oily substance (100 g) which gave primarily one slower moving spot on the thin layer chromatogram using different solvent systems.

Carolenalin Monoacetate (**2**).—Carolenalin (5 g) was acetylated with acetic anhydride and pyridine for 24 hr at room temperature to yield after two crystallizations from ethyl acetate 3.53 g of monoacetate **2**: mp 160–161°; $[\alpha]^{25}D$ – 91.7° (c 1.002, MeOH); uv (EtOH) end absorption; ir bands at 3580 (hydroxyl), 1760 (γ-lactone), 1740 (acetyl), and 1640 cm^{-1} (unsaturation).

Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 66.23; H, 7.69.

Carolenalin Diacetate (**3**).—Carolenalin (5 g) was acetylated with acetic anhydride and pyridine at room temperature for 72 hr to give a mixture of mono- and diacetates **2** and **3**. The latter was isolated by column chromatography on silica gel (100 g) using benzene and benzene–chloroform as eluents. Appropriate fractions were combined to yield after recrystallization from chloroform–*n*-hexane 1.2 g of the diacetate **3**: mp 146–148°; uv (EtOH) end absorption; ir bands at 1762 (γ-lactone) and 1740 cm^{-1} (double strength, acetyl).

Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48. Found: C, 64.77; H, 7.48.

Catalytic Hydrogenation of Carolenalin Monoacetate (**2**). **A. Dihydrocarolenalin Monoacetate** (**4**).—A solution of carolenalin monoacetate (200 mg) in methanol (15 ml) was hydrogenated at room temperature and atmospheric pressure using platinum oxide as catalyst. After 2 hr the catalyst was removed by filtration and the solvent was evaporated *in vacuo* to yield a residue. This residue was crystallized from *n*-hexane–ether (1:1) and recrystallized from ether containing a small amount of *n*-hexane to give the pure dihydrocarolenalin monoacetate (**4**) as colorless prisms (13 mg), mp 221–222°.

Anal. Calcd for $C_{17}H_{26}O_5 \cdot {}^1/_2H_2O$: C, 63.95; H, 8.15. Found: C, 64.19; H, 8.18.

B. Acid 5.—The filtrate after the removal of **4** was further concentrated to give another crystalline product which, upon recrystallization from *n*-hexane containing a small amount of ether, afforded the acid **5** as colorless needles (136 mg): mp 125–126°; ir bands at 3590 (hydroxyl), 1725 (acetyl), and 1700 cm^{-1} (acid).

Anal. Calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03. Found: C, 65.29; H, 9.05.

Methylation of Acid 5.—The acid **5** (54 mg) was methylated with diazomethane in the usual manner. The product crystallized and was collected and recrystallized from *n*-hexane–ether (1:1) to give 50 mg of the methyl ester **6** as colorless needles: mp 87–88°; ir bands at 3590 (hydroxyl) and 1725 cm^{-1} (double strength, ester and acetyl carbonyl).

Anal. Calcd for $C_{18}H_{30}O_5$: C, 66.26; H, 9.20. Found: C, 66.07; H, 9.32.

Oxidation of Carolenalin (**1**). **Keto Acid 7**.—A solution of carolenalin (250 mg) in acetone (20 ml) was cooled to 10–12° with stirring and treated with 0.5 ml of Jones reagent. After 10 min the solution was diluted with water and extracted with chloroform. The chloroform extract was washed with water, dried (Na_2SO_4), and evaporated to afford a crystalline residue which was recrystallized from ether to give **7** as colorless prisms (190 mg): mp 171–172°; ir bands at 3500 (broad, hydroxyl), 1765 (γ-lactone), and 1710 cm^{-1} (acid).

(29) Although carolenin and carolenalin could not be induced to crystallize, purification has been achieved by repeated column chromatography over silica gel.

Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.57; H, 7.46.

Methylation of Keto Acid 7.—The keto acid **7** was methylated in the manner described for compound **6**. The product formed colorless oil **8**: ir bands at 1765 (γ-lactone), 1730 (ester), and 1710 cm^{-1} (methyl ketone).

Carolenalin Acetonide (**9**).—To a solution of carolenalin (100 mg) in acetone (10 ml) was added *p*-toluenesulfonic acid (5 mg). After 5 min at room temperature the reaction mixture was diluted with water and extracted with chloroform. The dried chloroform extract was evaporated to give an oil which was passed through a column of neutral alumina (3 g) and eluted with ether to yield **9** as a colorless oil (80 mg). Tlc analysis of this oil showed a single spot, although it could not be crystallized. It showed ir absorption at 1760 (γ-lactone) and 1655 cm^{-1} (unsaturation).

Treatment of Carolenalin (**1**) **with Sodium Periodate. Keto Aldehyde 10**.—A solution of carolenalin (418 mg) in ethanol (20 ml) was added to a solution of sodium periodate (500 mg) in water (2 ml) containing concentrated sulfuric acid (0.5 ml). After standing at 38–40° for 30 min the reaction mixture was diluted with water, extracted with chloroform, and dried (Na_2SO_4). The dried chloroform extract was evaporated to furnish a yellowish, oily substance (**10**) which could not be induced to crystallize. Compound **10** showed a single spot on tlc (ethyl acetate–acetone, 3:1) and had ir absorption at 1765 (γ-lactone), 2730, 2830, 2880 (weak), and 1720 cm^{-1} (aldehyde).

Dehydrogenation of Carolenalin (**1**).—A mixture of carolenalin (3.3 g) and 30% palladium on carbon (500 mg) was heated at 200–300° for 10 min and then at 300–320° for 7 min. After cooling, the reaction mixture was extracted with ether, and the ether extract was chromatographed on neutral alumina. The first 30 ml of the ether eluate was further rechromatographed on neutral alumina. Elution with *n*-hexane (50 ml) afforded **11** as a dark blue oil (37 mg) which was converted to the crystalline trinitrobenzene complex, mp 128–129° (ethanol), ir (Nujol) bands at 1615 and 1535 cm^{-1} (unsaturation).

Anal. Calcd for $C_{20}H_{19}O_6N_3$: C, 60.45; H, 4.82. Found: C, 60.24; H, 4.92.

A mixture melting point with authentic chamazulene–trinitrobenzene adduct[23] showed no depression and the ir spectra were identical.

Hydrolysis of Carolenin (**13**).—A solution of carolenin (130 mg) in methanol (3 ml) and 10% potassium hydroxide (0.6 ml) was refluxed for 40 min. The reaction mixture was diluted with water, acidified with concentrated hydrochloric acid, and extracted with chloroform. The chloroform extract was further washed with 5% sodium bicarbonate solution in order to separate the acidic and the neutral fractions. The neutral fraction (the chloroform extract) was dried (Na_2SO_4) and evaporated *in vacuo* to give an oil which showed a mixture of two compounds on a thin layer chromatogram. The separation of this mixture of compounds was achieved by preparative tlc (silica gel, ethyl acetate–acetone, 6:1). One of them (90 mg) was identified as carolenalin (**1**) by tlc and ir and nmr spectral comparison with the authentic sample. The other was obtained as a colorless oil (35 mg) which showed an nmr spectrum virtually identical with that of carolenalin except for the slight differences of the chemical shifts and coupling constants in the methyl group at the C-11 position. The C-11 methyl group, which was seen as a three-proton doublet at δ 1.19 (J = 7.5 Hz) in carolenalin, was shifted to 1.23 (J = 6.0 Hz). This oily substance was believed to be the C-11 epimer of carolenalin.

The acidic fraction (the aqueous sodium bicarbonate layer) was acidified with dilute hydrochloric acid and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and evaporated to yield an oil, which was converted to the crystalline *p*-phenylphenacyl ester in the usual manner. The crude crystalline product was purified by preparative tlc (silica gel, benzene) to give *p*-phenylphenacyl angelate (mp 81–83°, 20 mg) and *p*-phenylphenacyl tiglate (mp 87–90°, 4 mg),[25a] which were identified by direct ir comparison, respectively.

Registry No.—**1**, 38769-25-4; **2**, 38769-26-5; **3**, 38769-27-6; **4**, 38769-28-7; **5**, 38769-29-8; **6**, 38769-30-1; **7**, 38769-31-2; **8**, 38769-32-3; **9**, 38769-33-4; **10**, 38769-34-5; **11** trinitrobenzene salt, 4955-13-9; **13**, 38769-36-7; *p*-phenylphenacyl angelate, 16193-68-3; *p*-phenylphenacyl tiglate, 19451-66-2.

Synthesis of Chaminic Acid

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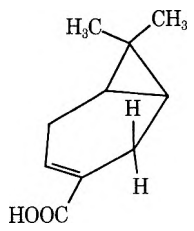
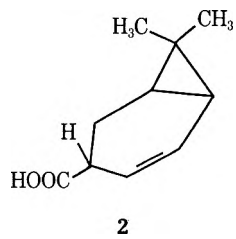
Chaminic acid, a bicyclic terpene from *Chamaecyparis nootkatensis*, has been synthesized. 5-Hydroxy-1,3-cyclohexanedicarboxylate, obtained by hydrogenating the benzenoid compound, is dehydrated with acetyl chloride to give in part the corresponding lactone and in part the acetate of the cyclic acid anhydride. Excess methylmagnesium chloride with either compound furnishes the same adduct, 5-hydroxy-1-(α-hydroxyisopropyl)cyclohexanecarboxylic acid. Chlorination to the α-chloroisopropyl derivative, esterification, and oxidation give rise to methyl 5-oxo-3-(α-chloroisopropyl)cyclohexanecarboxylate, which cyclizes with base to methyl 2-oxo-7,7-dimethylnorcarane-4-carboxylate. A double bond β,γ to the carboxyl group is then introduced by brominating the oxo compound, reducing the bromo ketone to bromohydrin, and eliminating the elements of hypobromous acid with zinc. The final step, yielding the desired *dl*-chaminic acid, consists in isomerizing the double bond to the α,β position with alkali. Arguments are presented allowing assignment of stereochemistry to the several intermediates.

Chaminic acid and chamic acid, terpenes isolated from the heartwood of the tree *Chamaecyparis nootkatensis*,[1] have been assigned the structures and absolute configurations as formulated in **1** and **2**.[2,3] The in-



1
chaminic acid



2
chamic acid

sect-repellent properties and the decay resistance of this heartwood may be attributed to one or possibly both of these compounds. We now wish to describe a synthesis of *dl*-chaminic acid[4] proceeding through cis or trans *dl*-chamic acid.[9]

The starting point was 5-hydroxyisophthalic acid (**3** diacid), readily accessible by alkali fusion of commercially available 5-sulfoisophthalic acid.[10] Catalytic hydrogenation (rhodium–alumina) of the dimethyl ester **3** saturated the ring to give dimethyl 5-hydroxy-1,3-cyclohexanedicarboxylate (**4**, 70%). Refluxing the corresponding diacid with acetyl chloride led to 5-acetoxy-1,3-cyclohexanedicarboxylic acid anhydride (**5**, 65%) plus the mixed anhydride of 5-hydroxy-1,3-cyclohexanedicarboxylic acid lactone (**6**, 10%). Excess methylmagnesium chloride either with anhydride **5** or with the acid lactone **7** from **6** furnished the same adduct **8** in good yield. Cold concentrated hydrochloric acid reacted selectively with the tertiary hydroxy group in **8** to form the tertiary chloride **9** (98%). After esterification of the carboxylic acid group in **9**, oxidation of the ring hydroxyl furnished cyclohexanone **10** (84%). This cyclized in the presence of potassium *tert*-butoxide to the desired bicyclic intermediate **11** (70%), with the cis form of **11** predominating.

The final stages of the synthesis called for removing the keto group of **11** and inserting an ethylenic link, as in **14**. Attempts to generate a double bond by elimination procedures using the cyclohexanol corresponding to cyclohexanone **11** failed. Thus low-temperature sulfonylation, expected to furnish the tosylate or the mesylate, gave products evidently with the three-membered ring opened. Neither the methyl xanthate nor the ethyl carbonate ester was obtained despite many trials under different conditions.[11] The tosylhydrazone derivative of ketone **11** could be obtained, but heating the lithium salt in aprotic solvent, instead of the desired olefin,[12] gave an actylenic material, probably methyl 7-methyl-6-octen-1-yne-4-carboxylate, as the major product.[13]

The sequence that succeeded in converting ketone **11** to chaminic acid (**1**) started with the bromination of **11** with phenyltrimethylammonium perbromide[14] to give α-bromo ketone **12**. Sodium borohydride reduced the bromo ketone to the bromohydrin **13**, which with

(1) B. Carlsson, H. Erdtman, A. Frank, and W. E. Harvey, *Acta Chem. Scand.*, **6**, 690 (1952).

(2) H. Erdtman, W. E. Harvey, and J. G. Topliss, *ibid.*, **10**, 1381 (1956).

(3) T. Norin, *Ark. Kemi*, **22**, 123 (1964).

(4) During the course of the work, a report appeared on the two-step conversion of 3-hydroxy-4-methylene-7,7-dimethylbicyclo[4.1.0]heptane to chaminic acid.[5] Since the bicyclo starting material had been derived before in several steps from Δ^3-carene,[6,7] whose preparation in turn can be traced back through many steps to simple starting materials,[8] a formal synthesis has already been achieved, although by a circuitous route.

(5) K. Gollnick and G. Schade, *Tetrahedron*, **22**, 133 (1966). Also see L. Borowiecki and W. Zacharewicz, *Rocz. Chem.*, **37**, 1143 (1963) [*Chem. Abstr.*, **60**, 4185 (1964)].

(6) S. P. Acharya and H. C. Brown, *J. Amer. Chem. Soc.*, **89**, 1925 (1967).

(7) P. J. Kropp, *ibid.*, **88**, 4926 (1966); K. Gollnick, S. Schroeter, G. Ohloff, G. Schade, and G. O. Schenck, *Justus Liebigs Ann. Chem.*, **687**, 14 (1965).

(8) O. Wallach, H. Kruse, and Fr. Kerkhoff, *ibid.*, **275**, 111 (1893); O. Wallach and H. Schrader, *ibid.*, **279**, 377 (1894); A. Baeyer, *Chem. Ber.*, **27**, 1915, 3485 (1894); K. N. Menon and J. L. Simonsen, *J. Indian Inst. Sci.*, **10A**, 1 (1927) [*Chem. Abstr.*, **21**, 3192 (1927)]; J. A. Simonsen, "The Terpenes," Vol. I, Cambridge University Press, New York, N. Y., 1957, pp 148, 150.

(9) Initial attempts by Cynthia L. Deyrup and Arthur P. Iodice at elaborating chaminic acid from *cis*-caronic acid, which already contains a three-membered ring, as well as attempts at forming both rings at once by application of an intramolecular diazo ketone cyclization directed specifically to ketone **11**, proved unsuccessful.

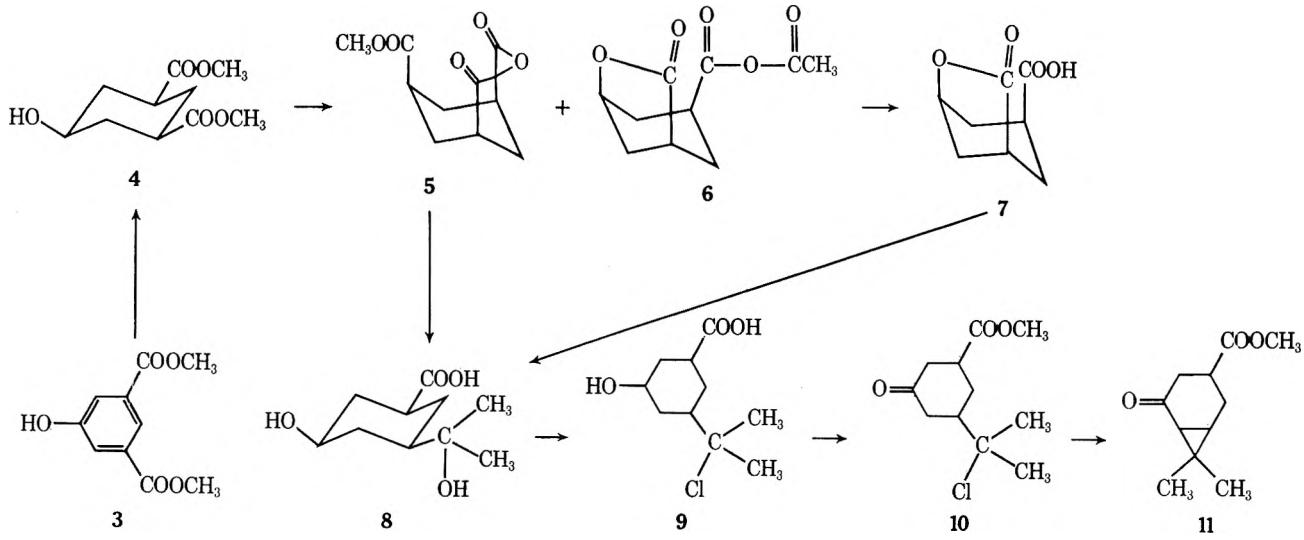
(10) *Cf.* K. Heine, *Chem. Ber.*, **13**, 491 (1880); H. Lonnies, *ibid.*, **13**, 203 (1880).

(11) Examples of the Chugaev elimination in related compounds may be found in U. T. Bhalerao, J. Plattner, and H. Rapoport, *J. Amer. Chem. Soc.*, **92**, 3429 (1970); W. Cocker, P. V. R. Shannon, and P. A. Staniland, *J. Chem. Soc. C*, 485 (1967); also see C. H. Depuy and R. W. King, *Chem. Rev.*, **60**, 431 (1960).

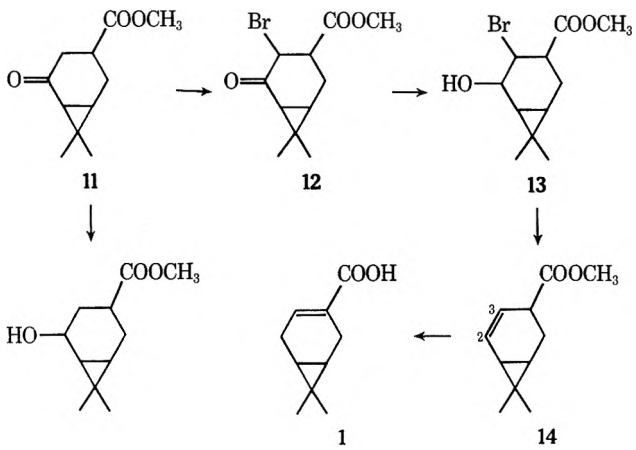
(12) Many examples are known: R. H. Shapiro and M. J. Heath, *J. Amer. Chem. Soc.*, **89**, 5734 (1967); W. G. Dauben, *et al.*, *ibid.*, **90**, 4762 (1968); F. Y. Edamura and A. Nickon, *J. Org. Chem.*, **35**, 1509 (1970).

(13) Analogous processes have been observed: *e.g.*, *cf.* J. W. Wheeler, R. H. Chung, Y. N. Vaishnov, and C. C. Shroff, *J. Org. Chem.*, **34**, 545 (1969); R. M. Coates and R. M. Freidinger, *Chem. Commun.*, 871 (1969); G. Ohloff and W. Pickenhagen, *Helv. Chim. Acta*, **54**, 1789 (1971).

(14) W. S. Johnson, J. D. Bass, and K. L. Williams, *Tetrahedron*, **19**, 861 (1963); D. Vorländer and E. Siebert, *Chem. Ber.*, **52**, 283 (1919); *cf.* C. Berger, M. Franck-Neumann, and G. Ourisson, *Tetrahedron Lett.*, 3451 (1968).



zinc in methanol eliminated the elements of HOBr to give either *cis*-chamic ester (**14**) or methyl chamate

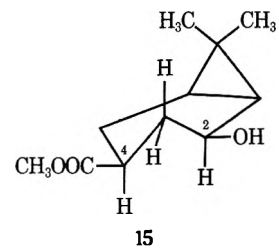


itself (**2**).[15] Instead of trying to purify this compound, it was isomerized with alkali[2] to give the desired *dl*-chaminic acid (**1**). The synthetic material corresponded well in its infrared, ultraviolet, and nuclear magnetic resonance spectra as well as in in melting point with the data[2,3] for the optically active forms.[16] The overall yield in the four-step **11** to **1** process came to 25% when manipulation at each stage was held to a minimum.

Stereochemistry.—Formation of lactone **7** establishes the fact that the hydroxyl group and one of the carboxy groups are on the same side of the cyclohexane ring; formation of acid anhydride **5** shows that both carboxy groups must be on the same side of the ring. These features, as well as the fact that anhydride **5** and lactone **7** both furnish the same Grignard adduct **8**, fix the all-cis configuration in hydrogenation product **4**. The reactions leading to intermediates **8**, **9**, and **10** involve no harsh conditions, so that we have assumed that the cis geometry is carried over to the chloro ketone **10**.

The base-catalyzed cyclization of **10** to **11** afforded two isomers **11** in a combined yield of 70%. That these were stereoisomers **16** and **19** rather than structural isomers was proved by their interconversion on contact with base.

Sodium borohydride reduces the cis keto ester **11** to the all-cis hydroxy ester **15** (60%) with both substituent groups equatorial. This assignment relied on published nuclear magnetic resonance data for the four geometric forms of 2-hydroxy-3,7,7-trimethylbicyclo[4.1.0]heptane.[6] In this set, when the hydroxyl is cis to the cyclopropane ring, the *gem*-dimethyl groups show chemical shifts differing by 7.5 and 13.5 Hz. In contrast, in both of the forms with hydroxyl trans to the cyclopropane ring, the chemical shift difference is 4.5 Hz. In our compound **15**, the chemical-shift difference is 8 Hz, a value that fits better with the cis assignment for the 2-hydroxyl group than the trans. Another indicator is the observed $W_{1/2}$ = 25 Hz for the C–H signal at position 2 in **15**, a value that fits the axial 2-H better than the equatorial.[17]



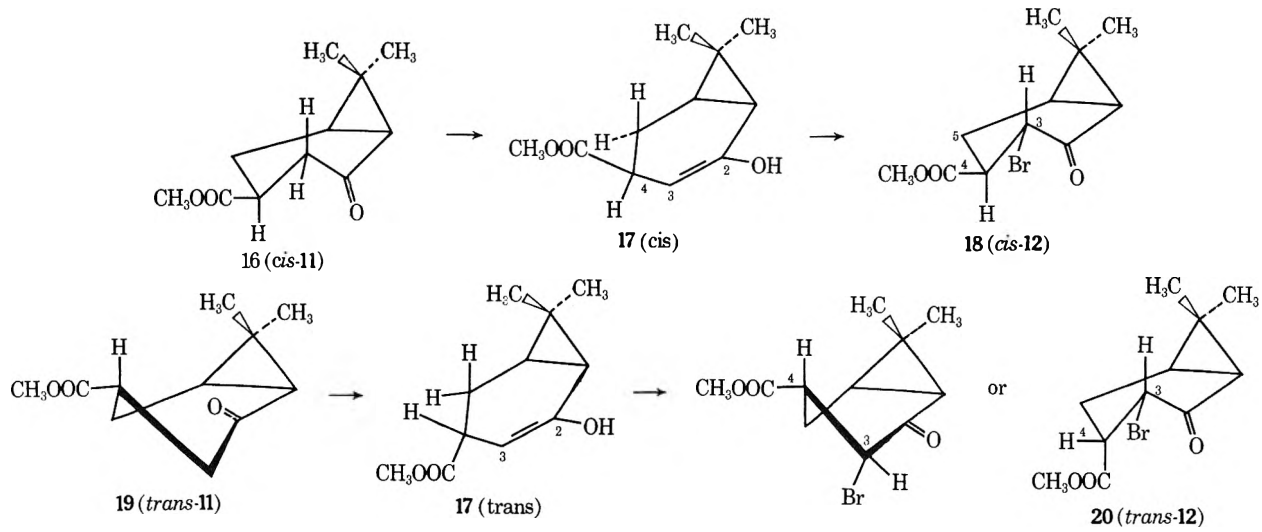
The stereochemical analysis for bromo compound **12** (**18**) leads to the conclusion that the 3-bromo and the adjacent 4-carbomethoxy group are both equatorial, and that the 4-carbomethoxy group is cis to the three-membered ring. The infrared ketone absorption peak for bromo compound **18** appears at a frequency 20 cm^{-1} higher than that for its precursor, **16**, a shift corresponding closely to those observed in equatorial α-bromocyclohexanones (as in **18**) but not to the shift for axial α-bromocyclohexanones (about 5 cm^{-1} to *lower* frequency).[18] So far as the geometric relation of the 3-bromo and 4-carbomethoxy groups in **18** is concerned, the coupling constant (12.5 Hz) of the 3-H with the 4-H corresponds far better to an axial–axial dihedral angle than to the angle for any equatorial–

(15) Related sequences have been reported. Thus *cf.* E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.*, **78**, 6267 (1956); M. Akhtar and S. Marsh, *Biochim. J.*, **102**, 462 (1967) [*Chem. Abstr.*, **66**, 52355b (1967)].

(16) Partial resolution (*ca.* 33%) of *dl*-chaminic acid into chaminic acid (dextro) and isochamic acid (levo) was achieved by fractionally recrystallizing the quinine salts. The optical rotatory dispersion curves of the partially resolved materials were close to being mirror images of each other.

(17) R. M. Silverstein and G. C. Bassler, "Spectroscopic Identification of Organic Compounds," Wiley, New York, N. Y., 1967.

(18) E. J. Corey, T. H. Topie, and W. A. Wozniak, *J. Amer Chem. Soc.*, **77**, 5415 (1955).



axial or equatorial–equatorial arrangement.[19] Accordingly the Br and $COOCH_3$ groups are taken as trans (equatorial–equatorial) as in **18**.

The assignments of cis and trans geometry to the two forms of keto ester **11** (see **16** and **19**) are made by considering the detailed steps in the subsequent bromination process. The intermediates in the bromination will be the enol *cis*-**17** derived from cis compound **16** and the enol *trans*-**17** derived from trans compound **19**. Dreiding models suggest that the enol forms have very little flexibility, and that both enols **17** will have their 4-C bent somewhat away from the *gem*-dimethyl groups. The alternate arrangement with the 4-C bent toward the *gem*-dimethyl grouping leads to appreciable steric interactions between the endo methyl group and the resulting upward-pointing axial group at position 4, no matter whether the axial group is carbomethoxy or hydrogen. Neither model *cis*-**17** nor *trans*-**17** offers much open space for approach of the bulky brominating agent from the side of the *gem*-dimethyl group, while both show more room on the opposite less hindered side. Accordingly in both enols, deposition of the bromo group at position 3 would be favored from the side opposite the *gem*-dimethyl groups, and therefore bromo ketone product **18** will be formed from cis precursor **16**, and product **20** from trans precursor **19**. Since only in conformation **18** are the bromo and ester groups disposed equatorially, both the starting material **16** and its bromo product **18** will have the ester group cis to the three-membered ring. The other cyclization product **19** (the isomer obtained in smaller amounts) accordingly has its ester group trans to the three-membered ring.

Experimental Section

General.—Melting points and boiling points are uncorrected. Thin layer chromatograms were obtained with commercially available supported layers of silica gel impregnated with a fluorescent material. Nuclear magnetic resonance spectra were recorded on a 60-MHz spectrometer. The analyses for elements were performed by Chemalytics, Inc., Tempe, Ariz., Galbraith Laboratories, Inc., Knoxville, Tenn., Scandinavian Microanalytical Laboratories, Herlev, Denmark, and Werby Laboratories, Inc., Boston, Mass.

Preparation and Alkali Fusion of 5-Sulfoisophthalic Acid.[10]—A mixture of isophthalic acid (85 g, 0.51 mol) and 20–23% fuming sulfuric acid (150 ml) was stirred and heated at 200–240° for 5 hr, or until quenching a few drops of the reaction mixture in cold water no longer gave a precipitate. The cooled mixture was poured over crushed ice, and the resulting solution was stirred until no more solid dissolved and filtered. Cooling the filtrate to −10° produced a slurry, which was filtered. The crystals of 5-sulfoisophthalic acid were dissolved in water, and the solution (*ca.* 300 ml) was treated with concentrated sulfuric acid (125 ml) and cooled again to −10°. The resulting crystals of 5-sulfoisophthalic acid were collected and sucked as dry as possible before dissolving them in absolute ethanol (550 ml). A solution of 112 g (2 mol) of potassium hydroxide in 500 ml of absolute alcohol was slowly introduced to precipitate the tripotassium salt, which was collected and dried in a vacuum oven overnight (251 g).

The tripotassium salt was added gradually to a melt of potassium hydroxide pellets (600 g) at 280°. Gas evolution was noted. The temperature was then held at 325° for 5 hr. The solid cooled melt was mixed with 1.4 l. of water, the alkaline mixture was filtered, and to the filtrate was added 840 ml of concentrated hydrochloric acid to pH 2. Filtration of the mixture at room temperature afforded crude 5-hydroxyisophthalic acid as a white solid. Several crystallizations from water produced 59 g of 5-hydroxyisophthalic acid, mp 305–306.5° (lit.[10] mp 284–285° for the dihydrate). The sample for analysis showed mp 296–299°.

Anal. Calcd for $C_8H_6O_5 \cdot {}^1/_2H_2O$: C, 50.01; H, 3.67. Found: C, 49.90; H, 3.46.

When a commercial source of 5-sulfoisophalic acid monosodium salt was located, the commercial material was used in the alkali fusion instead of the tripotassium salt, with essentially the same results.

Dimethyl 5-Hydroxyisophthalate (3).—A solution of the above hemihydrate of 5-hydroxyisophthalic acid (40 g, 0.21 mol) in 500 ml of anhydrous methanol containing 5 ml of concentrated sulfuric acid was refluxed for 2 days. After filtration, the clear solution was stripped of solvent. The residue was taken up in ethyl acetate (400 ml) and the solution was washed free of acids with aqueous sodium bicarbonate. The dried ($MgSO_4$) ethyl acetate solution was stripped of solvent, and then kept warm in an open flat dish until the resulting white, fluffy crystals of dimethyl 5-hydroxyisophthalate (**3**), mp 162–163.5° (lit.[10] mp 159–160°), reached constant weight (37 g, 85%): ir (mineral oil) 3360 (OH), 1710 and 1730 ($COOCH_3$), 1625, and 1610 cm^{-1}; ir ($CHCl_3$) 1710 (sh) and 1720 cm^{-1} (peak, $COOCH_3$); nmr (CD_3COCD_3) δ 8.12 (q, 1, J = 2 Hz, H-2), 7.71 (d, 2, J = 2 Hz, H-4 and H-6), 3.94 (s, 6, 2 $COOCH_3$), and 2.09–3.70 ppm (solvent impurity plus OH).

Anal. Calcd for $C_{10}H_{10}O_5$: C, 57.14; H, 4.80. Found: C, 57.14; H, 4.83.

Dimethyl 5-Hydroxy-1,3-cyclohexanedicarboxylate (4) by Hydrogenation of Dimethyl 5-Hydroxyisophthalate (3).—Suspensions of 5% rhodium-on-alumina catalyst (Englehardt Industries, Inc.) in methanol containing the isophthalate ester plus a small amount of acetic acid were shaken under hydrogen (55 psi) until either the correct amount of hydrogen had been absorbed or hydrogen uptake had stopped. Batches of ester ranging from 5 to 23 g were successfully converted, in each case with the weight of catalyst equal to $^1/_5$ the weight of ester, and with the

(19) *Cf.* F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1969, p 135.

volume of 1% acetic acid in methanol corresponding to 10–20 times the weight of ester. To avoid fire, it was necessary to have the methanol cooled to 0° before allowing it to come in contact with the catalyst. Hydrogenation required about 12 hr for the larger amounts.

Catalyst and solvent were removed from the hydrogenation mixtures. The combined residues from several preparations were dissolved in chloroform and were washed first with 10% aqueous potassium hydroxide and then with saturated salt solution. Solvent was distilled from the dried chloroform solution, and the remaining oily product was pumped at 0.1 mm for several hours. The combined yield (70.1 g) corresponded to a quantitative conversion. This material retained no sign of the 1625- or 1610-cm^{-1} absorptions attributable to the aromatic ring.

The hydrogenation product was divided into equal parts and each half was chromatographed through about ten times its weight of silica gel. The developing solvent was chloroform, followed by chloroform–ether mixtures with increasing proportions of ether, and finally ether. Fractions were monitored and were combined on the basis of thin layer chromatographic results (ether solvent). In this way was obtained a total of 13.9 g (22%) of dimethyl 1,3-cyclohexanedicarboxylate, R_f 0.89, and 48.6 g (70%) of dimethyl 5-hydroxy-1,3-cyclohexanedicarboxylate (4), R_f 0.43.

The structure of the lesser product, the hydrogenolysis product, bp 64–66° (0.05 mm), was assigned on the basis of its infrared absorption spectrum, ir ($CHCl_3$) 1740 cm^{-1} ($COOCH_3$), no absorption in the OH region.

The desired all-cis hydroxy diester 4 showed bp 116–128° (0.05) mm); ir ($CHCl_3$) 3500–3450 (OH) and 1735 cm^{-1} ($COOCH_3$); nmr (CCl_4) δ 1.0–2.6 (m, 8, ring protons at positions 1, 2, 3, 4, 6) and 3.54–3.65 ppm (m, 8, remaining protons dominated by CH_3O singlet at 3.65 ppm).

Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.89; H, 7.48.

Dichromate oxidation of dimethyl 5-hydroxy-1,3-cyclohexanedicarboxylate (4) afforded the corresponding keto diester (57%; mp 110–113° before recrystallization from ethyl acetate): mp 118.5–122°; ir ($CHCl_3$) 1730 cm^{-1}; nmr ($CDCl_3$) δ 1.0–2.61 (m, 8, ring, protons), 3.73 ppm (s, 6, 2 $COOCH_3$).

Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.08; H, 6.66.

Saponification of the hydroxy diester was accomplished by refluxing a mixture of 14.1 g (0.065 mol) of diester 4 and 5.5 g of sodium hydroxide with 40 ml of water for 1 day. After appropriate treatment of the reaction mixture, crystallization of the crude product from tetrahydrofuran–benzene gave 10.2 g (83%) of 5-hydroxy-1,3-cyclohexanedicarboxylic acid, mp 198–199°, ir (KBr pellet) 3600–2400 (OH and COOH) and 1715 cm^{-1} (shoulder at 1688 cm^{-1}).

Anal. Calcd for $C_8H_{12}O_5$: C, 51.06; H, 6.42. Found: C, 50.84; H, 6.36.

Acetyl Chloride Treatment of 5-Hydroxy-1,3-cyclohexanedicarboxylic Acid.—When a mixture of acetyl chloride (60 ml) and hydroxy diacid (12.7 g, 0.067 mol) was refluxed for 7 hr, the insoluble crystalline starting material gradually dissolved. Volatile material was removed, and the residue was pumped at 0.1 mm for several hours. The crystalline residue was fractionally recrystallized from acetone to give a total of 9.3 g (65%) of pure, less soluble 5-acetoxy-1,3-cyclohexanedicarboxylic acid anhydride (5), mp 190–193°, showing a single spot at R_f 0.72 (ethyl acetate), and approximately 1.0 g (10%) of less pure mixed anhydride 6 between acetic acid and 5-hydroxy-1,3-cyclohexanedicarboxylic lactone. The acetoxy anhydride 6 in chloroform showed infrared absorption peaks at 1810 and 1765 (cyclic anhydride) and 1740 cm^{-1} (acetate C=O); nmr (deuterated acetone) δ 5.03 (m, 1, H α to acetate), 3.03 (m, 2, H's α to anhydride carbonyls), 2.70 (broad s, 1, equatorial H at position 2), 2.12 (m, ring H's, 1.85 ppm (s, $OOCCH_3$).

Anal. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.68; H, 5.88.

Lactone 7 of 5-Hydroxycyclohexane-1,3-dicarboxylic Acid from the Mixed Acetic Anhydride 6.—The unpurified crystalline mixed anhydride as a solution in chloroform showed maxima at 1810 and 1765 (anhydride), 1780 (γ-lactone), and a shoulder at 1745 cm^{-1} (some of the acetoxy anhydride). Since this material lost acetic acid readily, it was not purified but instead was hydrolyzed directly to the lactone 7.

Refluxing a mixture of 3.3 g of the mixed anhydride–lactone with 10 ml of water for 45 min gradually dissolved the solid. Allowing the cooled solution to stand for 2.5 hr deposited 2.3 g of the desired lactone 7 of 5-hydroxy-1,3-cyclohexanedicarboxylic acid as crystals, mp 190–192°, ir (KBr pellet) 3500–2500 (COOH) and 1770 and 1685 cm^{-1} (γ-lactone and carboxyl carbonyls).

Anal. Calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92. Found: C, 56.59; H, 6.04.

5-Hydroxy-3-(α-hydroxyisopropyl)cyclohexanecarboxylic Acid (8) from Methylmagnesium Chloride and 5-Acetoxy-1,3-cyclohexanedicarboxylic Anhydride (5).—A solution of the acetoxy anhydride (5.0 g, 0.024 mol) in 300 ml of absolute tetrahydrofuran was added at 0° over 1.5 hr to methylmagnesium chloride (0.17 mol) in solution (58 ml) with the same solvent. The reaction mixture was stirred during addition and for 1 hr thereafter. Then saturated ammonium chloride solution (*ca.* 35 ml) was added dropwise to the mixture still at 0° until no further precipitate formed. The supernatant liquid was decanted from the heavy semisolid lower phase, which was then rinsed by decantation with two 20-ml portions of ether. Adding more ammonium chloride solution (*ca.* 150 ml) changed the clumped mass to discrete particles. This was followed with concentrated hydrochloric acid (to pH 2) and finally with enough water to dissolve all the solid. The acidic aqueous phase (*ca.* 400 ml) was ether extracted continuously for 1 week, with the solvent replaced every 2 days. Removal of ether from the combined extracts left crude product, which on recrystallization from concentrated water solution afforded pure, chunky, white crystals (85%) of 5-hydroxy-3-(α-hydroxyisopropyl)cyclohexanecarboxylic acid (8): mp 166.5–168°; ir (KBr pellet) 3600–2400, with sharper maxima at 3530 and 3375, 1705 cm^{-1}.

Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.55; H, 9.03.

5-Hydroxy-3-(α-hydroxyisopropyl)cyclohexanecarboxylic Acid (8) from Methylmagnesium Chloride and the Lactone 7 of 5-Hydroxycyclohexane-1,3-dicarboxylic Acid.—A solution of lactone 7 (0.50 g, 0.003 mol) in 65 ml of absolute tetrahydrofuran was added dropwise to a stirred tetrahydrofuran solution of methylmagnesium chloride (5.4 ml of 2.8 *M*, 0.016 mol) at 0° over a period of 15 min. After the mixture had been stirred further for 21 hr, product was isolated essentially as described before. Recrystallizations from water gave 5-hydroxy-3-(α-hydroxyisopropyl)cyclohexanecarboxylic acid (0.36 g, 60%), mp 166–167.5°. When this product was mixed with the same material prepared from the anhydride, the melting point was 167.5–168.5°. The infrared absorption curves were indistinguishable.

5-Hydroxy-3-(α-chloroisopropyl)cyclohexanecarboxylic Acid (9).—After 3.8 g of 5-hydroxy-3-(α-hydroxyisopropyl)cyclohexanecarboxylic acid (8) was dissolved in 60 ml of concentrated hydrochloric acid at 0° by stirring, the solution was stored cold for 16 hr. Filtration afforded the desired chloro compound 9, which was dried overnight under reduced pressure to give 3.7 g (98%) of crystalline product, mp 165.5–166.5°. Although this was suitable for use in the next step, a sample (mp 168.5–169°) for analysis was prepared by recrystallizations from acetone–hexane.

Anal. Calcd for $C_{10}H_{17}ClO_3$: C, 54.42; H, 7.76; Cl, 16.06. Found: C, 54.23; H, 7.87; Cl, 16.21.

This material 9, pelleted with potassium bromide, showed infrared absorptions at 3500 and 2500 (broad), 3420, and 1705 cm^{-1}.

The ketone corresponding to hydroxy acid 9 was prepared by introducing 14 drops of chromium(VI) solution to a solution (0°) of chlorohydroxy acid 9 (107 mg) in 10 ml of acetone. The oxidant was made up by adding 2.3 ml of concentrated sulfuric acid to 2.88 g of chromium(VI) trioxide dissolved in 4 ml of water and then diluting with water to 10 ml. After 0.5 hr at 0°, the reaction mixture was filtered, and volatiles were removed from the filtrate. Water (4 ml) was added to the residue, which was then extracted thoroughly with chloroform. The dried extract was treated with a little isopropyl alcohol, the resulting blue mixture was filtered, and the filtrate was stripped of solvent. Crystallizations from benzene–hexane gave white crystals (76 mg, 71%) of 5-oxo-3-(α-chloroisopropyl)cyclohexanecarboxylic acid (acid corresponding to 10): ir (KBr) 3700–2500, 1725, 1685 cm^{-1}; ir ($CHCl_3$) 1750 and 1710 cm^{-1}. Material melting at 129.5–130° was analyzed.

Anal. Calcd for $C_{10}H_{15}ClO_3$: C, 54.92; H, 6.91, Cl, 16.21. Found: C, 54.89; H, 6.65; Cl, 16.17.

Methyl 5-Oxo-3-(α-chloroisopropyl)cyclohexanecarboxylate (10) by Oxidation of the 5-Hydroxyl Ester.—The starting ester,

methyl 5-hydroxy-3-(α-chloroisopropyl)cyclohexanecarboxylate, prepared from acid 9 with diazomethane in ether–methanol, showed ($CHCl_3$) absorptions at 3600 (sharp) and 1730 cm^{-1}; nmr signals ($CDCl_3$) were seen at δ 3.66 (s, $COOCH_3$), *ca.* 3.55 (m, HCOH), 3.51 (s, OH), 1.56 [s, $C(CH_3)_2$], 2.5–1.0 ppm (m, ring H's).

With the temperature at 5–8°, acid chromium trioxide solution (12 ml, see above) was added over 45 min to a stirred solution of this ester (9.4 g, 0.037 mol) in 200 ml of acetone. After another 15 min at 0°, the mixture was filtered, the crushed solids were rinsed with acetone, and the combined filtrates were evaporated. Water (20 ml) was added to the residue, which was thoroughly extracted with chloroform. The extracts were washed twice with small portions of 5% bicarbonate and twice with saturated aqueous sodium chloride, and then treated with solid sodium sulfate, some sodium bicarbonate, and a few milliliters of isopropyl alcohol. Removal of solvent from the dry solution left a crystalline residue, which when rinsed with hexane and air dried weighed 8.2 g and showed mp 67.5–68° (softening at 65°). Chromatography through a 2 × 50 cm column of silica gel with chloroform as solvent was monitored by thin layer chromatography. Removal of solvent, etc., furnished 7.3 g (84%) of one-spot methyl 5-oxo-3-(α-chloroisopropyl)cyclohexanecarboxylate (10): mp 69–71.5°; ir ($CHCl_3$) 1735 and 1715 cm^{-1}; nmr ($CDCl_3$) δ 3.69 (s, 3, $COOCH_3$), 2.56 (m, H's next to keto group), 2.7–1.0 (m, H's at positions 1, 2, 3), 1.58 ppm [d, J = 3 Hz, $ClC(CH_3)_2$]. Integration of the signals from 2.56 to 1.0 ppm showed 14 protons as demanded.

Methyl 2-Oxo-7,7-dimethylnorcarane-4-carboxylate (11) by Cyclization of Methyl 5-Oxo-3-(α-chloroisopropyl)cyclohexanecarboxylate (10).—Approximately 1.2 g (0.03 g-atom) of clean pieces of potassium was dissolved in 40 ml of boiling *tert*-butyl alcohol that had been distilled from calcium hydride. A solution of methyl 5-oxo-3-(α-chloroisopropyl)cyclohexanecarboxylate (10, 3.7 g, 0.016 mol) in 30 ml of benzene was added dropwise over a period of 25 min to the *tert*-butoxide solution kept cool with a bath of cold water. The milky amber reaction mixture was stirred at room temperature for 45 min. Some ice was added and the mixture was evaporated to a volume of *ca.* 5 ml, diluted with an equal volume of water, and extracted twice with ether. The aqueous layer at 0° was brought to pH 2 with 6 *N* hydrochloric acid, and the acid mixture was extracted with ether to remove the carboxylic acid product. The extract, after rinsing with saturated aqueous salt solution and drying, was stripped of volatiles to yield *ca.* 3.0 g of yellow viscous 2-oxo-7,7-dimethylnorcarane-4-carboxylic acid (acid corresponding to 11): ir ($CHCl_3$) 1710 (COOH), 1680 (cyclopropyl ketone), and 900 cm^{-1} (cyclopropane ring).

Esterification with diazomethane afforded the methyl ester in near-quantitative yield. This was chromatographed over 100 g of silica gel, with ether–hexane (15:85) as solvent, and with fractions combined with the help of thin layer chromatographic monitoring.

Methyl *cis*-2-oxo-7,7-dimethylnorcarane-4-carboxylate (11), R_f 0.72 (hexane–ether–methanol, 20:10:1), was isolated in 42% yield (1.3 g): ir ($CHCl_3$) 1730, 1680, and 900 cm^{-1}; uv (95% ethanol at 1 × 10^{-4} *M*) λ_{max} 208 nm (log ε 3.72); nmr (CCl_4) δ 3.62 (s, 3, $COOCH_3$), 1.16 (s, *gem*-dimethyl), and 1.0–3.0 ppm (m, cyclohexane protons). The signals from 1.16 to 3.0 ppm integrated to 13 protons. A sample of 11 for analysis was prepared by a bulb-to-bulb distillation.

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.25; H, 8.19.

Methyl *trans*-2-oxo-7,7-dimethylnorcarane-4-carboxylate (11), R_1 0.53, was obtained in 0.63-g yield. Together with a second fraction (0.24 g) showing the presence of a trace of extraneous material at R_f 0.62, the yield of the trans isomer was 28%: ir ($CHCl_3$) 1725 and 1675 cm^{-1}, with the fingerprint region substantially different from that of the cis isomer; uv (95% ethanol, 8 × 10^{-5} *M*) λ_{max} 208 nm (log ε 3.67); nmr (CCl_4 with bulb-to-bulb distilled material) δ 3.64 (s, 3, $COOCH_3$), 1.0–3.0 (m, cyclohexane ring protons), 1.16 (s, exo CH_3), 1.08 ppm (s, endo CH_3). The signals from 3.0 to 1.08 ppm integrated to 13 protons as required.

Interconversion of Cis and Trans Isomers of Methyl 2-Oxo-7,7-dimethylnorcarane-4-carboxylate (11). A. Trans to Cis.—The trans isomer 19 (0.63 g, 0.0033 mol) in 10 ml of *tert*-butyl alcohol was added slowly to a solution of potassium (0.4 g, 0.01 g-atom) in 15 ml of *tert*-butyl alcohol. The dark brown solution was stirred at room temperature under nitrogen for 40 min. After part of the solvent was removed, the concentrated solution was added dropwise to 7 ml of cold 6 *N* hydrochloric acid. Adding an excess of solid sodium bicarbonate neutralized the mixture, which was then distilled until all the *tert*-butyl alcohol had been removed. Addition of a few drops of aqueous sodium hydroxide raised the pH from 8 to 9. The basic solution was rinsed twice with ether and acidified with cooling to pH 2, and the acid products were extracted thoroughly with ether. The combined extracts were dried, and the viscous yellow residue (0.55 g) dissolved in methanol was esterified with ethereal diazomethane. After several hours, the filtered solution was evaporated to give 0.51 g of methyl esters. Column chromatography though silica gel in a 1.2 × 50 cm column using 700 ml of ether–hexane (15:85) followed by 950 ml of ether–hexane (20:80) gave several fractions, one of which consisted of homogeneous methyl *cis*-2-oxo-7,7-dimethylnorcarane-4-carboxylate (16, 0.10 g, 19%) with R_f 0.78, and another of the trans isomer 19 (0.15 g, 27%) with R_f 0.48. The identity of the cis and trans isomers was established by R_f comparisons and by infrared absorption curves, which were identical, respectively, with those of the previously isolated compounds.

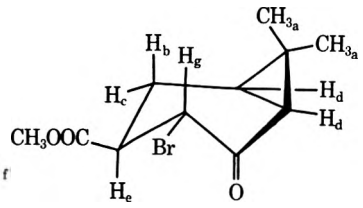
B. Cis to Trans.—The cis isomer 16 (26 mg) in 2 ml of dry *tert*-butyl alcohol was stirred with 5 ml of a 0.77 solution of potassium *tert*-butoxide for 1 hr. Processing similar to that described above gave 25 mg of reesterified crude methyl esters. Thin layer chromatography (two developments) showed four spots; the R_f values of two of the darkest corresponded to those of authentic cis and trans esters spotted on the same plate.

Methyl 2-Hydroxy-7,7-dimethylnorcarane-4-carboxylate by Reduction of the Corresponding Oxo Compound 11.—A cold solution of sodium borohydride (46 mg, 1.2 mmol) in 4 ml of methanol was added to 98 mg (0.5 mmol) of methyl *cis*-oxo-7,7-dimethylnorcarane-4-carboxylate (11) dissolved in cold methanol (5 ml). The mixture was allowed to come to room temperature and was stirred further for 3 hr. Solvent was removed, 4 ml of water was added to the residue, and the mixture, held at 0°, was brought to pH 2–3 with hydrochloric acid. The aqueous phase was extracted with ether, which after rinsing with 5% aqueous bicarbonate and then water was dried ($MgSO_4$). Removal of all solvent left 78 mg of product which showed no ketone absorption at 1675 cm^{-1}. Column chromatography through 1.2 g of silica gel using first benzene and then 1:1 benzene–chloroform as developing solvents gave fractions containing a total of 58 mg of one-spot, solvent-free hydroxy ester (60%): ir ($CHCl_3$) 3600 and 3450 (OH) and 1730 cm^{-1} ($COOCH_3$): nmr ($CDCl_3$) δ 4.32 (m, $W_{1/2}$ = 25 Hz), 3.66 (s, $COOCH_3$), 1.66 (s, OH), 0.9–2.5 (m, cyclohexane ring protons at 1, 3, 4, 5, 6), 1.2 (s, exo CH_3), 1.09 ppm (s, endo CH_3). The first two signals corresponded to 4 protons, all the others to 14. A sample for analysis was prepared by bulb-to-bulb distillation.

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.59; H, 9.23.

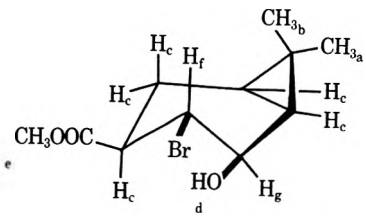
Methyl 3-Bromo-2-oxo-7,7-dimethylnorcarane-4-carboxylate (12).—A 0° solution of methyl *cis*-2-oxo-7,7-dimethylnorcarane-4-carboxylate (11, 0.45 g, 2.3 mmol) in 20 ml of freshly distilled tetrahydrofuran was treated with portions of phenyltrimethylammonium perbromide[14] (total weight 0.90 g, 2.4 mmol; mp 114–115.5°). After 50 min of stirring, another 20 mg of perbromide was added and the mixture was stirred further for 5 min.

The mixture, containing a white precipitate, was poured into an ice-cold water solution of 5% sodium bicarbonate (15 ml) plus 0.1 *N* sodium thiosulfate (16 ml). The separated bromination product 12 was taken up in ether, and the ether solution was washed, dried, and stripped of solvent. The viscous residue deposited crystals after standing at 0°, and, after trituration with a small amount of cold methanol, furnished 0.19 g (30%) of crystalline methyl 3-bromo-2-oxo-7,7-dimethylnorcarane-4-carboxylate (12), mp 112.5–113.5°. Other preparations gave the same product with mp 115–115.5°. Assay with the help of infrared absorption showed that the mother liquor contained appreciable additional amounts of the desired product; the estimated total yield was *ca.* 50%. The crystalline material showed ir ($CHCl_3$) 1730 ($COOCH_3$) and 1695 cm^{-1} (α-bromo ketone); uv (95% alcohol, 8 × 10^{-5} *M*) λ_{max} 212 nm (log ε 3.575); nmr ($CDCl_3$) δ 4.53 (d, J_{eg} = 12.5 Hz, 1, H_g), 3.75 (s, 3, H_f), 3.21 (sextet, J_{eg} = J_{eb} = 12.5 Hz; J_{ec} = 5 Hz, 1, H_e), 1.7 (m, H_d), 1.5–2.5 (m, H_b and H_c), 1.21 ppm (s, H_a). The signals on the high-field side of δ 2.5 ppm integrated to 10 protons, as required.



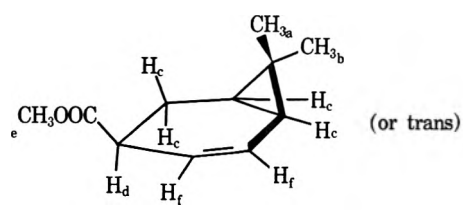
Anal. Calcd for $C_{11}H_{15}BrO_3$: C, 48.01; H, 5.49; Br, 29.02. Found: C, 47.97; H, 5.54; Br, 29.12.

Methyl 2-Hydroxy-3-bromo-7,7-dimethylnorcarane-4-carboxylate (13) from Oxo Compound 12.—Solid sodium borohydride (24 mg, 0.63 mmol) was added to an ice-cold solution of methyl 3-bromo-2-oxo-7,7-dimethylnorcarane-4-carboxylate (62 mg, 0.24 mmol) in methanol (7 ml). After 35 min, methanol was stripped, water was added to the residue, and the mixture was extracted thoroughly with ether. The oil obtained after removing ether from the dried extract weighed 63 mg (100%) and was taken as product **13**: ir ($CHCl_3$) 3670 and 3450 (OH) and 1730 cm^{-1} ($COOCH_3$), with the ketone peak at 1695 cm^{-1} missing; nmr ($CDCl_3$) δ 3.8–4.6 (m, 2, H_f and H_g), 3.68 (s, 3, H_e), 2.5 (m, H_d), 1.0–3.0 (m, H_c), 1.18 (s, H_b), 1.06 ppm (s, H_a). The signals other than those for H_e, H_f, and H_g integrated to 12 protons.



Bromohydrin **13** decomposes on standing; the infrared and nuclear magnetic resonance absorption curves of the decomposition product are consistent with those expected for methyl 3-isopropylbenzoate.

***dl*-Chaminic Acid (1).**—A solution of 63 mg of unpurified bromohydrin **13** in 10 ml of methanol was refluxed for 22 hr with 0.64 g of "activated" granular zinc.[20] After standing overnight, solvent was removed and the residue was extracted with chloroform. The liquid (58 mg) left after stripping solvent from the filtered extract was taken as the Δ^2-unsaturated product **14**: ir ($CHCl_3$) 3500 (broad, weak band corresponding to a low concentration of OH), 1725 ($COOCH_3$), and 1640 and 1600 cm^{-1} (weak). The nuclear magnetic resonance absorption curve closely resembled that published[3] for natural chamic acid when the acid-ester differences are taken into account. Preparative layer chromatography over silica gel using 200:15:1.5 hexane–ether–methanol afforded material with ir ($CHCl_3$) peaks at 1725 ($COOCH_3$) and 1640 and 1655 cm^{-1} (isolated and conjugated double bonds); nmr ($CDCl_3$) δ 5.84 (m, *ca.* 2, H_f), 3.68 (s, 3,



H_e), 3.15 (m, H_d), 2.5–0.8 (m, H_c), 1.08 (s, H_b), 0.92 ppm (s, H_a). The integration ratio for the H_e and H_f protons to all the rest was *ca.* 5:11 as required by methyl 7,7-dimethylnorcar-2-ene-4-carboxylate (**14**). A very small peak at δ 0.73 ppm confirmed the infrared evidence in suggesting the presence of a small proportion (less than 5%) of methyl chaminate in this material.

Instead of isolating the Δ^2 isomer **14**, the mixture was converted to the conjugated chaminic acid (**1**) as follows. A mixture of crude Δ^2 isomer (49 mg) with 25% aqueous sodium hydroxide was refluxed for 2 hr. The cooled homogeneous system was rinsed with ether (discarded), and after acidification (pH 2) was extracted thoroughly with ether. Removal of all solvent from the dried ether extract left a tacky residue (26 mg, 55%) which showed a nuclear magnetic resonance spectrum almost identical with that obtained subsequently for pure *dl*-chaminic acid (**1**). Purification of this material was accomplished by thick layer chromatography (50:60:1 hexane–ether–acetic acid) followed by rinsing the crystals so obtained with a few drops of hexane. The resulting *dl*-chaminic acid (**1**) showed mp 101–103°.

Preparative Directions for *dl*-Chaminic Acid (1) from Methyl 2-Oxo-7,7-dimethylnorcarane-4-carboxylate (11).—Bromination of the oxo compound **11** (0.69 g) essentially as described before gave 0.25 g of crystalline bromo ketone **12**, mp 112.5–113.5°, as well as an oily impure fraction (see below). The crystalline bromo ketone was reduced with excess sodium borohydride to give 0.26 g of semicrystalline bromohydrin **13**. This was treated with zinc in methanol for 42 hr; the filtered (Celite) solution was then refluxed for 2.5 hr in the presence of 0.75 g of sodium hydroxide with 2 ml of water. Methanol was removed under reduced pressure, water was added, and the alkaline solution was processed as before to give 0.13 g of semicrystalline *dl*-chaminic acid (**1**). Two crystallizations from benzene afforded crystalline product (0.06 g), mp 102–104°, in 40% overall yield from the crystalline bromo ketone.

When the above oily impure bromo ketone was put through the same steps crude *dl*-chaminic acid (**1**) was obtained, which was then chromatographed through a small column of silica gel (1:5 ether–hexane), with the less pure fractions being rechromatographed. *dl*-Chaminic acid (**1**) was obtained, mp 97.5–100.5° (0.11 g). A finel recrystallization of the combined crystalline products from methanol gave 0.14 g (25% from methyl *cis*-2-oxo-7,7-dimethylnorcarane-4-carboxylate, **11**), mp 104.5–105.5°. The value reported for the optically active forms is 105–106°.[2,3] The synthetic material showed uv (1.1×10^{-4} *M* in 95% alcohol) λ_{max} 218 nm (log ϵ 3.871) [lit.[2] λ_{max} 218 nm (log ϵ 3.860)]; ir ($CHCl_3$) 3500–2400 (broad), 1680, 1647, 1655 cm^{-1} (sh) (the spectrum was the same as that described for natural chaminic acid[2]); nmr ($CDCl_3$) δ 10.7 (broad s, COOH), 7.05 (broad s, 1, vinyl H), 2.33 (m, 4, 2 ring CH_2's), 1.1–0.5 (m, cyclopropane H's), 1.07 (s, exo CH_3), 0.73 ppm (s, endo CH_3). The signals for the two methyl groups plus the two cyclopropane H's integrated to eight protons.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.27; H, 8.49. Found: C, 72.03; H, 8.76.

Formation of the quinine salt of racemic chaminic acid followed by fractional crystallization from benzene–hexane appeared to offer a practical resolution method for the levorotatory enantiomer (isochamic acid). Fractional precipitation of the less soluble isochamic salt by adding hexane to a benzene solution of racemic material containing a deficiency of quinine left the uncombined chaminic acid in solution. Appropriate processing, including crystallizations from methanol, afforded the partially resolved materials in good recovery. With rotations determined using methanol as solvent, the partially resolved chaminic acid, mp 104.5–105°, showed $[\alpha]_{590}$ *ca.* +2.1° (lit.[2] +6°); the partially resolved isochamic acid, mp 102.5–103°, showed $[\alpha]_{590}$ *ca.* −2.3 (lit.[2] −6°). Thus the extent of resolution was 30–40%. Resolution to optical purity was not pursued.

Registry No.—**1**, 38859-06-2; **2** methyl ester, 38859-07-3; **3**, 13036-02-7; **3** free acid, 618-83-7; **4**, 38859-08-4; **4** corresponding keto derivative, 38859-09-5; **4** free acid, 38859-10-8; **5**, 38859-11-9; **6**, 38859-12-0; **7**, 38859-13-1; **8**, 38859-14-2; **9**, 38859-15-3; **9** methyl ester, 38859-17-5; **10**, 38859-18-6; **10** free acid, 38859-16-4; *cis*-**11**, 38859-19-7; *trans*-**11**, 38859-20-0; **11** corresponding hydroxy derivative, 38858-06-9; *cis*-**12**, 38859-21-1; **13**, 38859-22-2; **14**, 38859-23-3.

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A Novel Method for the Degradation of the Carbon Chain of Organic Acids and Their Derivatives

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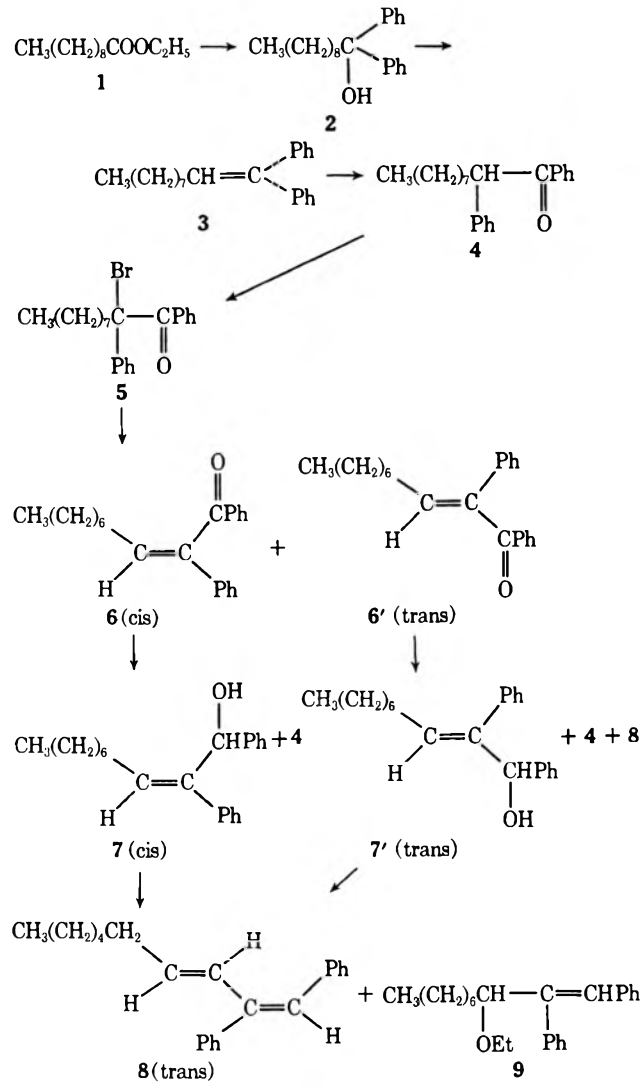
A convenient scheme for the stepwise degradation of ethyl caprinate (1) is described, which allows the removal of either one, two, or three carbon fragments from the chain, affording high yields of the corresponding carbonyl compounds. The method may have important applications in the transformations of steroids, lipids, and other natural products.

The utility of side chain degradative schemes in the syntheses, modification, and structural elucidation of natural products is well known.[2] The same type of reactions also find useful applications in the transformations of lipids.[3] However, none of the available methods[4-8] for degrading carboxylic acids give particularly attractive yields.

Furthermore, to our best knowledge, there is no satisfactory degradative scheme which permits the elimination of two carbon atoms at a time. The present paper describes a practical and flexible procedure for removing one, two, or three carbon atoms. The key step makes use of a rearrangement worked out before[9] and found to be successful on a variety of substrates, including some steroids. The individual steps in the degradative sequence are outlined in Scheme I.

SCHEME I



Results and Discussion

A commericial sample[10] of pure (99% by glc) ethyl caprinate (1) was allowed to react with an ether solution of phenylmagnesium bromide, prepared in the usual way. After purification of the crude alcohol by column chromatography, a nearly quantitative yield (96%) of 1,1-diphenyl-1-decanol (2) was obtained. Dehydration of the alconol was achieved in refluxing acetic anhydride. After suitable work-up and purification of the crude product by column chromatography, a sufficiently pure sample of 1,1-diphenyl-1-decene (3) was obtained. The yield based on the ester 1 was 85%. The identity of the product was confirmed by infrared and nmr spectroscopy and by elemental analysis.

The olefin 3 was without any further purification subjected to the conditions of the Kakis reaction,[9] which converted it smoothly to 1,2-diphenyl-1-decanone (4).

After purification of the crude product by recrystallization from methanol followed by thin layer chromatography, a 90% yield (76.5% overall) of pure (mp 56.5–57°) ketone 4 was obtained. The identity of the ketone was established by infrared, ultraviolet, and nmr spectroscopy and by elemental analysis.

The following two steps in the degradation sequence involved the α-bromination[11] of 1,2-diphenyl-1-decanone 4 followed by the collidine dehydrobromination[12] of the resulting 1,2-diphenyl-2-bromo-1-decanone (5).

Both reactions were nearly quantitative. The identity of the products was in each case confirmed by infrared and nmr spectroscopy. The ketones 6 and 6′ were further identified by elemental analysis.

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(12) J. J. Beereboom, C. Djerassi, D. Ginsburg, and L. Fieser, *J. Amer. Chem. Soc.*, **75**, 3500 (1953).

As expected, the collidine dehydrobromination of **5** produced a mixture of cis (**6**) and trans (**6′**) α,β-unsaturated ketones which were separated by thin layer chromatography on fluorescent silica plates and characterized by nmr.[13] The ratio of cis to trans product was about 1:1.6.

The reduction of the isomeric ketones **6** and **6′** was accomplished by means of the specialized reagent[14] $AlNa(OCH_3OCH_2CH_3)_2H_2$, producing the allylic alcohols **7** and **7′**, respectively. After purification by thin layer chromatography a 75% yield of the cis (**7**) and a 50% yield of the trans (**7′**) alcohol was obtained. Thus the combined yield of alcohols was 62.5% (48% overall, *i.e.*, based on **1**).

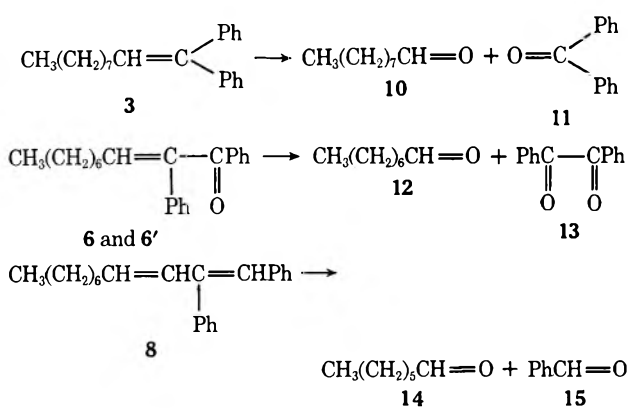
A small quantity (*ca.* 6%) of the ketone **4** was also isolated, presumably stemming from 1,4 reduction of the conjugated ketones **6** and **6′**.

The three components were readily separable by thin layer chromatography.

The alcohols **7** and **7′** were subsequently dehydrated with ethanolic hydrochloric acid.[15] Thus a 70% (34% overall) yield of 1,2-diphenyl-1,3-decadiene (**8**) was obtained whose nmr spectrum was compatible with the trans,trans structure shown. In addition a 20% yield of 1,2-diphenyl-3-ethoxy-1-decene (**9**) was isolated. Attempting to minimize the formation of this side product, the dehydration of the alcohols **7** and **7′** was also tried with methanol and isopropyl alcohol solvents. However, the yields were in these cases substantially lower than those obtained from the ethanolic hydrochloric acid dehydration.

Thus it can be seen that the sequence of reactions described above and summarized in Scheme I generates compounds **3**, **6** and **6′**, and **8**, which can in turn be degrated by ozonolysis with the corresponding loss of one, two, and three carbon fragments, respectively. These possibilities are summarized in Scheme II.

SCHEME II



We have in fact carried out the ozonolysis of these compounds by standard procedures[16] and have isolated and identified all the fragments. Thus the ozonolysis of 1,1-diphenyl-1-decene (**3**) resulted in the formation of nonanal (**10**) and benzophenone (**11**). Similarly compounds **6** and **6′** yield octanal (**12**) and benzil (**13**) and compound **8** yields heptanal (**14**) and benzaldehyde (**15**). To facilitate the separation and identification of the ozonolysis products the mixtures were treated with the Wanzlick reagent,[17] which selectively converts the aldehydes into crystalline derivatives. These derivatives were easily separable by chromatography, and their melting points were in agreement with those reported in the literature.[17] Furthermore, mixture melting points with authentic samples showed no depression. In the case of heptanal and benzaldehyde additional confirmation was obtained by glc and by preparing the 2,4-dinitrophenylhydrazone derivatives. Again the melting points were in agreement with those reported in the literature.

We estimate that the typical ozonolysis yields were about 80%. Thus we have achieved a two-carbon fragment degradation with an overall yield of 60% for the six-step process.

The corresponding overall yield for the removal of three carbon atoms was about 28% for the eight-step process.

The removal of one carbon atom from the chain involves three steps and proceeds with an overall yield of about 70%.

In view of the above, we feel that the procedure we have developed is superior to the existing degradative schemes, not only because of the higher yields but also because in most cases substantial portions of unchanged starting materials can be easily recovered. Thus the process lends itself well to recycling, which may be significant in industrial terms.

From the foregoing discussion, it can be concluded that a useful degradative method has been developed with potential important applications in the chemistry of natural products. This possibility is currently under investigation.

Experimental Section

General.—Melting points were taken on a Köfler apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer. Ultraviolet spectra were recorded on a Beckman Model DK2A spectrophotometer. Nmr spectra were determined on a Jeol Model C60H spectrometer using tetramethylsilane as internal standard and are reported in parts per million. Gas chromatographic analysis was carried out on a Loenco Model 160 gas chromatograph equipped with a LAC 446, 8-ft column. Microanalysis were performed by the microanalysis service of C. N. R. S. at the Gif Sur Yvette laboratories in France.

1,1-Diphenyl-1-decanol (2).—The preparation of this compound involved the standard addition of phenylmagnesium bromide (0.5 mol) to a commercial sample[10] of ethyl caprinate (**1**) (10 g, 0.05 mol, 99% pure).

After hydrolysis of the reaction mixture and decomposition with a saturated solution of ammonium chloride, *ca.* 20.3 g of crude product was obtained (yellow oil).

After purification by column chromatography over silica (Merck, 0.05–0.2 mm) using a pentane–ether mixture as the eluent (10:1), 15 g of the pure alcohol (96%) was obtained.

1,1-Diphenyl-1-decene (3).—This compound was prepared by dehydrating a sample of the alcohol **2** (15 g) in refluxing acetic anhydride for a period of 10 hr. After removal of the solvents by rotatory evaporation, the crude product was purified by column chromatography over silica (Merck, 0.05–0.2 mm) using petroleum ether (bp 48–55°) as the eluent. Thus 12.4 g (85%) of pure 1,1-diphenyl-1-decene was obtained. The sample showed the following physical data: ir (CCl_2=CCl_2) 3080, 3060, 3020, 1600, and 700 cm^{-1}; nmr ($CDCl_3$) δ 0.88 (3 H, multiplet,

(13) C. Pascual, J. Meir, and W. Simon, *Helv. Chim. Acta*, **49**, 164 (1966).

(14) V. Bazant, M. Capka, M. Cerny, V. Chralorsky, K. Kochloef, M. Krans, and J. Mulek, *Tetrahedron Lett.*, 3303 (1968).

(15) R. Ginsig and A. D. Gross, *J. Org. Chem.*, 1761 (1966).

(16) R. L. Augustine, "Oxidation," Marcel Dekker, New York, N. Y., 1969, p 303.

(17) H. W. Wanzlick and W. Löckel, *Ber.*, **86**, 1463 (1953).

methyl), 1.28 (12 H, singlet, $-CH_2-$), 2.1 (2 H, multiplet, $-CH_2$ allylic), 6.09 (1 H, triplet, ethylenic, J = 7.5 Hz), 7.23 (10 H, aromatic protons).

The above nmr constants were in agreement with those reported in the literature.[18]

Anal. Calcd for $C_{22}H_{28}$: C, 90.35; H, 9.65. Found: C, 90.37; H, 9.46.

1,2-Diphenyl-1-decanone (4).—A sample (2 g) of the olefin **3** was converted to 1,2-diphenyl-1-decanone (**4**) by the Kakis method.[9] The crude product (2.4 g) was then purified by recrystallization from methanol, followed by thin layer chromatography of the mother liquors over fluorescent silica using a petroleum ether–ether mixture (6:1) as the eluent. Thus 1.9 g (90%) of pure (mp 56.5–57°) 1,2-diphenyl-1-decanone (**4**) was obtained. Confirmation of structure was obtained by the following physical data: ir (CCl_4) 3090, 3070, 3030, 1690, 1450, and 690 cm^{-1}; nmr ($CDCl_3$) δ 0.85 (3 H, multiplet, $-CH_3$), 1.25 and 2 [14 H, singlet, $(-CH_2)_7$], 4.53 (1 H, triplet, H α to ketone, J = 7.5 Hz), 7.25–8.1 (10 H, aromatic protons); uv (95% EtOH) 244 mμ (ϵ 11,180).

Anal. Calcd for $C_{22}H_{28}O$: C, 85.66; H, 9.15; O, 5.19. Found: C, 85.38; H, 8.98; O, 5.39.

1,2-Diphenyl-2-bromo-1-decanone (5).—A sample (1 g) of the ketone **4** was brominated by the method of Baudry.[11] After work-up 1.23 g (99%) of chromatographically pure product was obtained: ir (CCl_4) 3090, 3070, 3030, 1685, 1450, 1225, doublet at 695–685, and 655 cm^{-1}; nmr ($CDCl_3$) δ 0.85 (3 H, multiplet, $-CH_3$), 1.2 [12 H, multiplet, $(-CH_2)_6$], 2.4 (2 H, multiplet, $-CH_2CBrPh$), 7.15–7.85 (10 H, aromatic protons).

***cis*- and *trans*-1,2-Diphenyl-1-keto-2-decene (6 and 6').**—Dehydrobromination of a sample (1.25 g) of compound **5** by collidine[12] afforded a mixture (0.92 g, 99%) of *cis*- and *trans*-1,2-diphenyl-1-keto-2-decene. Analytical thin layer chromatography of the mixture on silica–silver nitrate (7%) plates with petroleum ether–ether (30:1) eluent showed that it was practically pure.

Separation was achieved on fluorescent silica preparatory plates by multiple elutions with the above solvent mixture (R_f of trans compound **6**, R_f of cis compound **4**).

Thus 330 mg of the pure cis isomer **6** and 530 mg of the pure trans isomer **6'** were obtained: ir (CCl_2CCl_2) 3090, 3070, 3030, 1675, 1600, 1450, 1215, and 690 cm^{-1}; nmr ($CDCl_3$) for trans compound δ 0.85 (3 H, multiplet, $-CH_3$), 1.25 [10 H, multiplet, $(-CH_2)_5$], 2.1 (2 H, multiplet, $-CH_2-$ allylic), 6.28 (1 H, triplet, ethylenic, J = 7.5 Hz), 7.25–8.2 (10 H, aromatic protons); for cis compound δ 0.87 (3 H, multiplet, $-CH_3$), 1.27 [10 H, multiplet, $(-CH_2-)_5$], 2.25 (2 H, multiplet, $-CH_2-$ allylic), 6.5 (1 H, triplet, ethylenic, J = 7.5 Hz), 7.2–8 (10 H, aromatic protons); uv (95% EtOH) for cis 245 mμ (ϵ 18,900); for trans 245 mμ (ϵ 24,000).

Anal. Calcd for $C_{22}H_{26}O$: C, 86.23; H, 8.55; O, 5.22. Found for cis: C, 86.28; H, 8.77; O, 5.40. Found for trans: C, 86.40; H, 8.52; O, 5.45.

1,2-Diphenyl-2-decen-1-ol (7 and 7'). A. Reduction of Compound 6.—A sample of compound **6** (250 mg) was reduced with bis(2-methoxyethoxy)sodium aluminum hydride, $AlNa(OCH_3OCH_2CH_3)_2H_2$, by a procedure similar to that of Bazant, *et al.*[14] On work-up 250 mg of crude product was obtained. Separation was achieved by thin layer chromatography on fluorescent silica plates with a petroleum ether–ether mixture (5:1) as the eluent. Thus 190 mg (75%) of the pure alcohol **7** was obtained. The chromatography also afforded 20 mg of ketone **4**. **7** had ir ($CCl_2{=}CCl_2$) 3620, 3080, 3030, 1600, 1490, 1450, and 700 cm^{-1}; nmr ($CDCl_3$) δ 0.87 (3 H, multiplet, $-CH_3$), 1.23 [10 H, $(-CH_2-)_6$], 1.95 (2 H, multiplet, $-CH_2-$ allylic), 5.45 (1 H, singlet, $-CHOH$), 5.92 (1 H, triplet, ethylenic H, J = 7.5 Hz), 7.1–7.2 (10 H, aromatic protons).

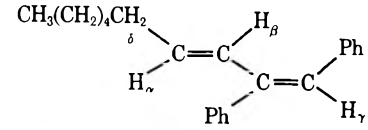
Anal. Calcd for $C_{22}H_{28}O$: C, 85.66; H, 9.15; O, 5.19. Found: C, 85.68; H, 9.19; O, 5.20.

B. Reduction of Compound 6'.—A reduction of a sample (500 mg) of compound **6'** by a procedure identical with the above afforded 440 mg of a crude product. The purification of the product mixture and separation of the components was carried out as before. Thus 250 mg (50%) of alcohol **7'**, 30 mg of ketone **4**, and 20 mg of the dehydration product 1,2-diphenyl-1,3-decadiene (**8**) were obtained in a pure state. **8** had ir same as **7**; nmr ($CDCl_3$) δ 0.9 (3 H, multiplet, $-CH_3$), 1.35 [10 H, $(-CH_2-)_5$], 2.25 (3 H, multiplet, allylic $-CH_2-$ and $-OH$), 5.88 (2 H, triplet, 6:3:1, $-CHOH$ and $CH=$), 7.1–7.3 (10 H, aromatic protons).

Anal. Calcd for $C_{22}H_{28}O$: C, 85.66; H, 9.15; O, 5.19. Found: C, 85.95; H, 9.28; O, 5.14.

1,2-Diphenyl-1,3-decadiene (8).—Dehydration of either alcohol **7** or **7'** (200 mg) by means of ethanolic hydrochloric acid[15] gave after work-up a mixture of two products (200 mg). The mixture was separated on fluorescent silica plates with a mixture of petroleum ether–ether (20:1) as the eluent.

Thus 130 mg (70%) of pure diene **8** (R_f 9) and 45 mg (20%) of 1,2-diphenyl-3-ethoxy-1-decene (**9**) (R_f 7.5) were obtained. Diene **8** had ir ($CCl_2{=}CCl_2$), 3090, 3070, 3030, 1600, 1490, 1470, 1450, and 700 cm^{-1}; nmr ($CDCl_3$) δ 0.88 (3 H, multiplet, $-CH_3$),



1.3 [8 H, $(-CH_2-)_4$], 2.1 (2 H, multiplet, $-CH_2-$ allylic), two triplets centered at 5.27 (H_α, $J_{\alpha,\delta}$ = 7.5, $J_{\alpha,\beta}$ = 16 Hz); 6.36 (H_β, doublet, $J_{\alpha,\beta}$ = 16 Hz), 6.42 (H_α, singlet), 6.65–7.5 (10 H, aromatic protons).

Anal. Calcd for $C_{22}H_{26}$: C, 90.98; H, 9.02. Found: C, 90.84; H, 9.14.

Compound **9** had ir (CS_2) 3080, 3060, 3030, 1080, 760, and 700 cm^{-1}; nmr ($CDCl_3$) δ 0.88 (3 H, multiplet, $-CH_3$), 1.05–1.7 [12 H, large, $(-CH_2-)_6$ and triplet due to $-CH_3$ of CH_3CH_2O-], quadruplet centered at 3.65 due to $-CH_2-$ of $-OCH_2CH_3$, 3.9 (1 H, $-CHOEt$), 6.7 (1 H, singlet, $RC{=}CH-$), 7–7.6 (10 H, aromatic protons).

Ozonolysis.—All of the ozonolysis reactions were carried out as follows. The reactants were dissolved in a mixture of methanol and methylene chloride (2:3). The solution was then ozonized until the appearance of a blue color (5–10 min).

Decomposition was accomplished by stirring the product mixture with a solution of potassium iodide in glacial acetic acid.

The mixtures were then extracted with ether and the organic phase was decolorized by washing with a sodium thiosulfate solution and a saturated sodium bicarbonate solution.

The combined ether extracts were then dried over anhydrous magnesium and sodium sulfates.

Removal of the solvents by rotatory evaporation afforded the crude mixtures of the ozonolysis products. In some instance direct chromatographic separation of these products proved difficult. Consequently, the mixtures were treated with freshly prepared Wanzlick reagent,[17] which converted all the aldehyde components of the mixtures to the crystalline dianilinoethane derivatives, easily separable by chromatography. Purification was achieved by recrystallization from methanol.

Thus from the ozonolysis of 1,1-diphenyl-1-decene (**3**), nonanal (**10**) was isolated as the dianilinoethane derivative (mp 54–55°) along with benzophenone (mp 46.5–48°).

Similarly the ozonolysis of 1,2-diphenyl-1-keto-2-decenes (**6** and **6'**) afforded octnal **12** as the dianilinoethane derivative (mp 53.5–54.5°) and benzil **13** (mp 95–96°).

Finally the dianilinoethane derivatives of heptanal (**14**) (mp 77–78°) and benzaldehyde (mp 136–137°) were isolated from the ozonolysis of 1,2-diphenyl-1,3-decanone (**8**).

In all of the above cases the observed melting points were in agreement with those reported in the literature.[17] Confirmation was obtained by mixture melting points with authentic samples.

In the last ozonolysis additional confirmation was obtained by gas chromatography of the original mixture against known standards.

Registry No.—**1**, 110-38-3; **2**, 21236-83-9; **3**, 1530-27-4; **4**, 38821-25-9; **5**, 38821-26-0; **6**, 38821-29-3; **6'**, 38821-30-6; **7**, 38896-72-9; **7'**, 38896-73-0; **8**, 38821-31-7; **9**, 38821-28-2.

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(18) A. Jung and M. Brini, *Bull. Soc. Chim. Fr.*, 693 (1964).

Alkylation–Reduction of Carbonyl Systems. II. A Convenient Synthesis of Aromatic Hydrocarbons by the Alkylation–Reduction of Aromatic Ketones and Aldehydes[1]

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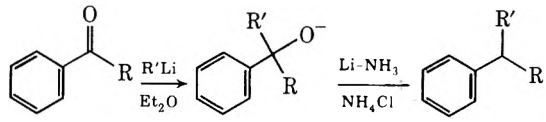
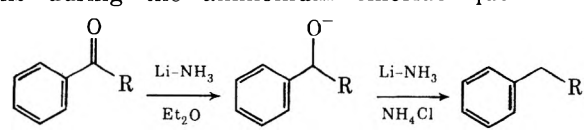
Aromatic hydrocarbons are prepared from aromatic ketones and aldehydes by alkylation with an organolithium reagent followed by lithium–ammonia reduction in the same reaction vessel without isolation of intermediates. Methylation–reduction yielded *p-tert*-butylethylbenzene from *p-tert*-butylbenzaldehyde, *p*-ethylisopropylbenzene from *p*-isopropylbenzaldehyde, 1-methylindan from 1-indanone, 1,1,3-trimethylindan from 3,3-dimethylindanone and 5-chloro-3,3-dimethylindanone, 1,1,3,4,5,6,7-heptamethylindan from 3,3,4,5,6,7-hexamethylindanone, 1-methyltetralin from 1-tetralone, 1,1-diphenylethane from benzophenone, 9-methylxanthene from xanthenone, 9-methylfluorene from fluorenone, and 2,4-diphenylpentane from dibenzoylmethane. Butylation–reduction yielded *p-tert*-butylpentylbenzene from *p-tert*-butylbenzaldehyde, *p*-isopropylpentylbenzene from *p*-isopropylbenzaldehyde, 1-butylindan from 1-indanone, 1-butyltetralin from 1-tetralone, and 1,1-diphenylpentane from benzophenone. Phenylation–reduction yielded *p-tert*-butylbenzylbenzene from *p-tert*-butylbenzaldehyde, *p*-isopropylbenzylbenzene from *p*-isopropylbenzaldehyde, 1-phenylindan from 1-indanone, 1-phenyltetralin from 1-tetralone, triphenylmethane from benzophenone, and 9-phenylfluorene from fluorenone.

Recently we introduced the concept of tandem alkylation–reduction of aromatic ketones and aldehydes to aromatic hydrocarbons.[3] At that time we demonstrated the feasibility of the procedure, which involves the lithium–ammonia reduction of a benzyl alkoxide generated *in situ* by alkylation, with a few methylation–reduction examples. We now wish to report our completed study in this area which includes the alkylation–reduction of a reasonable sampling of aromatic ketones and aldehydes using phenyllithium, *n*-butyllithium, and methyllithium as illustrative alkylating agents.



The advantages of the method over such classics as the alkylation–dehydration–catalytic reduction procedure are that the entire sequence is carried out in the same reaction vessel without isolation or purification of intermediates, the procedure consumes only a few hours, and the isolated yield of the aromatic hydrocarbon is in most cases excellent.[4]

The basis for this work evolved from the results of some of our earlier studies on the lithium–ammonia reduction of aromatic ketones to aromatic hydrocarbons.[5] It was demonstrated that aromatic ketones are reduced to benzyl alkoxides in lithium–ammonia solutions and the benzyl alkoxides were protonated and reduced to the corresponding aromatic hydrocarbons during the ammonium chloride quench.[6] It seemed reasonable to assume that a benzyl alkoxide, generated by other methods, such as alkylation of an aromatic carbonyl compound, should also be reduced to an aromatic hydrocarbon when subjected to this metal–ammonia procedure. The potential advantages of such a sequence were immediately obvious.



The general procedure is to generate the benzyl alkoxide in a metal–ammonia reaction vessel[7] by the addition of the aromatic ketone or aldehyde to the organolithium reagent in ether. Ammonia is subsequently distilled into the vessel, followed by the addition of lithium wire; and then the resulting mixture is cautiously quenched with ammonium chloride.

The organolithium reagents used were commercial methyllithium (ether), *n*-butyllithium (hexane), phenyllithium (ether–benzene); and phenyllithium (ether) and *n*-butyllithium (ether) generated *in situ* from the corresponding bromides and lithium foil. All the organolithium reagents that were generated in ether or are commercially available in ether were extremely satisfactory; however, slight modifications had to be made for those in hexane or benzene. In these cases a mixture of alkylated aromatic hydrocarbon and alkylated benzyl alcohol resulted when the normal amount of lithium (3 equiv) was used in the reduction step. However, this problem was overcome by the use of excess lithium (6 equiv) and vigorous stirring during the quench step. Evidently the slight amount of hexane in the commercial *n*-butyllithium and the benzene in the commercial phenyllithium results in a two-phase system.[8]

Table I is a listing of aromatic ketones and aldehydes that have been alkylated–reduced to aromatic hydrocarbons by this method. All products gave satisfactory spectral and analytical data and, in some cases, were compared with authentic samples. Minor products are observed when the alkylation step or the reduction step is incomplete. The former yields unalkylated aromatic hydrocarbon,[5a] which is removed by distillation, and the latter yields alkylated benzyl alcohol, which is conveniently removed by column

(1) This investigation was supported in part by Research Grant CA12984 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) Taken in part from the Master of Science Thesis of S. D. L. submitted to The Graduate School, Rutgers University.

(3) Part I: S. S. Hall and S. D. Lipsky, *J. Chem. Soc., Chem. Commun.*, 1242 (1971).

(4) As a matter of fact, the purity of some of the ether extracts made further purification steps unproductive.

(5) (a) S. S. Hall, S. D. Lipsky, F. J. McEnroe, and A. P. Bartels, *J. Org. Chem.*, **36**, 2588 (1971); (b) S. S. Hall, S. D. Lipsky, and G. H. Small, *Tetrahedron Lett.*, 1853 (1971).

(6) For a discussion of the possible mechanism see ref 5a.

(7) For a useful general discussion of metal–ammonia exper.mental techniques see R. L. Augustine, Ed., "Reduction," Marcel Dekker, New York, N. Y., 1968, pp 98–105.

(8) In the latter case there is also the possibility that the benzene is being reduced, and thereby consuming some of the lithium.

TABLE I

ALKYLATION–REDUCTION OF AROMATIC KETONES AND ALDEHYDES

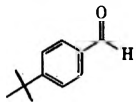
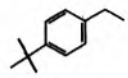
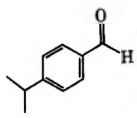
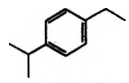
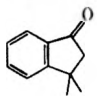
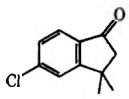
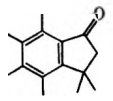
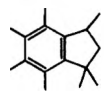
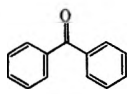
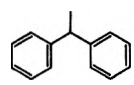
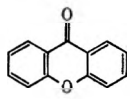
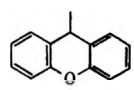
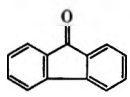
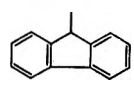
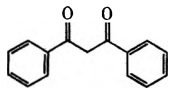
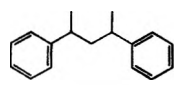
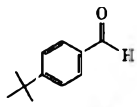
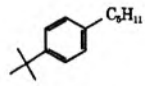
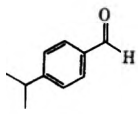
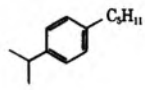
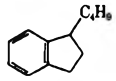
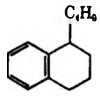
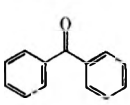
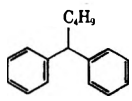
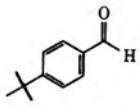
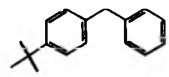
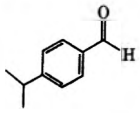
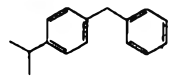
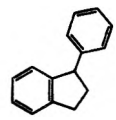
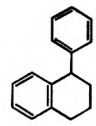
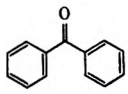
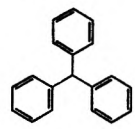
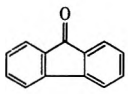
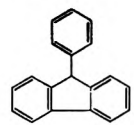
Aromatic carbonyl compound	Registry no.	Organolithium reagent	Alkylation-reduction Product	Registry no.	% yield		Minor product (s)[a]		Comments
					Analytical[a]	Isolated[b]	Unalkylated aromatic hydrocarbon	Alkylated benzyl alcohol	
	34032-41-2	MeLi		7364-19-4	100	94			*c*
	122-03-2	MeLi		4218-48-8	100	95			*c*
	83-33-0	MeLi		767-58-8	100	95			*c*
	26465-81-6	MeLi		2613-76-5	85	81	15		*c*
	30428-23-0	MeLi		38857-68-0	90	85	10		*d*
	30427-98-6	MeLi		38857-69-1	73	68	27		*c*
	529-34-0	MeLi		1559-81-5	80	78	20		*c*
	119-61-9	MeLi		612-00-0	100	95			*c*
	90-47-1	MeLi		38731-93-0	90	65	10		*e*
	486-25-9	MeLi		2523-37-7	73	67	13		*c, f*
	120-46-7	MeLi		1145-23-9	87	79		13	*g*
		BuLi		38857-73-7	78	66	22		*h, i*
		BuLi		38857-74-8	90	86	10		*h*
		BuLi		38857-75-9	90	89	10		*h, j*
		BuLi		38857-76-0	78	76	22		*k*
		BuLi		1726-12-1	77	70	23		*h, l*

TABLE I (*Continued*)

Aromatic carbonyl compound	Registry no.	Organolithium reagent	Alkylation-reduction Product	Registry no.	% yield		Minor product (s)[c]		Comments
					Analytical[a]	Isolated[b]	Unalkylated aromatic hydrocarbon	Alkylated benzyl alcohol	
		PhLi		16251-99-3	96	93	4		*h*
		PhLi		886-58-8	90	88	10		*m*, *n*
		PhLi		26461-03-0	100	97			*h*
		PhLi		3018-20-0	82	80		18	*h*
		PhLi		519-73-3	100	97			*m*
		PhLi		789-24-2	98	93	2		*h*

[a] Analyzed by glpc using a 6 ft × 0.25 in. 10% Apiezon L on Chromosorb W (60–80, AW-DMCS) column in a flame detector instrument at a 40-ml/min flow rate. All samples were injected at a reasonable temperature, followed by a 10-min post-injection interval, and then programmed at 10°/min to 290° and held at limit for 0.5 hr. [b] Isolated from an aluminum oxide column by eluting with petroleum ether. [c] Reaction conditions are those described in the Experimental Section for the methylation–reduction of benzophenone (synthesis of 1,1-diphenylethane) using commercial MeLi and 3 equiv of lithium. [d] Five equivalents of lithium was used for the reduction sequence because of the presence of chlorine. [e] Because of the insolubility of this ketone in ether, a solution of the ketone in 20 ml of THF was added to 2 equiv of MeLi in 10 ml of THF. [f] Plus an unidentified product (14%). [g] In this experiment 2.5 mmol of ketone was used. [h] The organolithium reagent was generated *in situ* in ether from *n*-butyl bromide or bromobenzene and 3 equiv of lithium was used for the reduction. See phenylation–reduction of indanone (synthesis of 1-phenylindan) in Experimental Section. [i] When commercial *n*-BuLi and 3 equiv of lithium were used *p*-*tert*-butylpentylbenzene (5%) and 1-(4′-*tert*-butylphenyl)pentanol (95%) were formed. [j] When commercial *n*-BuLi and 6 equiv of lithium were used 1-butylindan (73%) and indan (27%) were formed. [k] Commercial *n*-BuLi and 6 equiv of lithium were used. See phenylation–reduction of benzophenone (synthesis of triphenylmethane) in Experimental Section. [l] When commercial *n*-BuLi and 3 equiv of lithium were used 1,1-diphenylpentane (12%), 1,1-diphenylpentanol (68%), and benzophenol (20%) were formed. [m] Commercial phenyllithium (ether–benzene) and 6 equiv of lithium were used. See phenylation–reduction of benzophenone (synthesis of triphenylmethane) in Experimental Section. [n] When commercial phenyllithium and 3 equiv of lithium were used *p*-isopropylbenzylbenzene (56%), *p*-isopropylphenylphenyicarbinol (30%), and *p*-isopropyltoluene (14%) were formed.

chromatography. Since excess organolithium reagent was used the incomplete alkylation suggests that some enolization or reduction of the carbonyl compound may have occurred during the alkylation step.[9] Incomplete reduction seems to result when the intermediate benzyl alkoxide is splattered on the walls of the reaction vessel and is not in solution during the quench.

Experimental Section[10]

Alkylation–Reduction General Comments.—The entire reaction sequence was performed under a prepurified nitrogen atmosphere which is connected by a T tube to the assembly and an oil bubbler. All glassware was oven-dried, cooled to room temperature in a large box desiccator, and then quickly assembled. The commercial organolithium reagents, methyllithium (5.1% in ether), *n*-butyllithium (15.1% in hexane), and phenyllithium (19.7% in ether–benzene), were obtained from Foote Mineral Co. Anhydrous ether was used directly from freshly opened containers. Anhydrous ammonia was distilled into the reaction vessel. Lithium wire (0.125 in., 0.01% Na, Ventron Corp.) was wiped free of oil and rinsed in petroleum ether (bp 38–58°) just prior to use. All alkylated aromatic hydrocarbon products gave satisfactory spectral and analytical data, and in some cases were compared with authentic samples. Three alkylation–reductions are described to illustrate the general methods. The first, 1,1-diphenylethane, exemplifies the procedure using an organolithium reagent commercially available in ethyl ether. The second, 1-phenylindan, demonstrates the use of an organolithium reagent which is generated *in situ* in ether. The last, triphenylmethane, uses an organolithium reagent which is commercially available in solvents other than ether.

1,1-Diphenylethane.—To a stirred ethereal solution of methyllithium (7.5 mmol, 4.8 ml of a 5.1% ether solution diluted with 10 ml of ether) was slowly added a solution of 0.908 g (5 mmol) of benzophenone in 10 ml of ether in a metal–ammonia reaction

(9) J. D. Buhler, *J. Org. Chem.*, **38**, 904 (1973).

(10) Spectral measurements were determined with the following instruments: ir, Beckman Model IR-10; nmr, Varian Associates Model A-60; mass spectra, Perkin-Elmer Model 270 with a Varian Associates Model 620/i computer attachment. Gas chromatographic analyses (glpc) were performed on a Hewlett-Packard Model 5750 research chromatograph (flame detector) using a 6 ft × 0.25 in. 10% Apiezon L on 60–80 Chromosorb W (AW, DMCS) column. Separations and purifications were attained on absorption alumina (80–200 mesh) columns using petroleum ether (bp 38–58°). Further purification, when necessary, was accomplished by flash or short-path distillation.

vessel.[7] After 1 hr 25 ml of ammonia was distilled into the mixture; this was then followed by the addition of 105 mg of lithium wire (15 mg atoms, six pieces). After 15 min the dark-blue color was discharged by the rather cautious addition (*ca.* 5 min) of ammonium chloride[11] (*ca.* 1.5 g) and the ammonia was allowed to evaporate. After the residue had been partitioned between aqueous NaCl and Et_2O, the organic layer was dried, concentrated, and analyzed by glpc. After chromatography (alumina, petroleum ether) a colorless liquid (0.86 g, 95%) was isolated which was identical with an authentic sample of 1,1-diphenylethane.[12]

1-Phenylindan.—Into a metal–ammonia reaction vessel[7] containing 210 mg of lithium wire (30 mg-atoms, 12 pieces which had been hammered to a foil) in 10 ml of ether was slowly added a solution of 1.18 g (7.5 mmol) of bromobenzene in 7 ml of ether. After 1 hr a solution of 658 mg (5 mmol) of 1-indanone in 8 ml of ether was slowly added and the mixture was stirred for an additional 1 hr. Ammonia (*ca.* 25 ml) was distilled into the mixture and, once the dark-blue color of the mixture was established, *ca.* 1.6 g of ammonium chloride was cautiously added[11] (*ca.* 4 min) to discharge the blue color and the ammonia was allowed to evaporate. After the residue had been partitioned between aqueous NaCl and ether, the organic phase was dried, concentrated, and analyzed (glpc). Following chromatography (alumina, petroleum ether) white crystalline material (935 mg, 97%) was isolated and compared with an authentic sample prepared by a classical procedure.[13]

Triphenylmethane.—To a solution of 7.2 mmol of phenyllithium (4.5 ml of a 19.7% ether–benzene solution) in 10 ml of ether in a metal–ammonia reaction vessel[7] was added, dropwise and with stirring, 908 mg (5 mmol) of benzophenone in 10 ml of ether. After 1 hr *ca.* 25 ml of ammonia was distilled into the mixture and then 210 mg of lithium wire (30 mg-atoms, 12 pieces) was quickly added. After 15 min *ca.* 2.9 g of ammonium chloride was cautiously added[11] (*ca.* 4 min) to discharge the dark-blue color and the ammonia was allowed to evaporate. The residue was partitioned between ether and aqueous NaCl, and the ethereal layer was dried, concentrated, and analyzed (glpc). Chromatography (alumina, petroleum ether) yielded 1.22 g (97%) of a white crystalline compound which was identical with a commercial sample of triphenylmethane.

Registry No.—MeLi, 917-54-4; BuLi, 109-72-8; PhLi, 591-51-5.

Acknowledgments.—The authors wish to thank Ms. Rose Marie Luethy and Mr. Paul P. Vallon, Givaudan Corp., Clifton, N. J., for the mass spectra, and Dr. Franz J. Scheidl, Hoffmann-La Roche Inc., Nutley, N. J., for the microanalyses.

(11) The ammonium chloride was most conveniently introduced by attaching a glass tube filled with the salt to a side arm with tygon tubing. When the ammonium chloride is to be added the tube is raised and tapped gently to smoothly introduce the quenching agent. Should this step start to become violent, the addition and the vigorous stirring should be momentarily stopped to avoid an eruption.

(12) J. S. Reichert and J. A. Nieuwland, *J. Amer. Chem. Soc.*, **45**, 3090 (1923).

(13) This is a good example of what we called a classic procedure (alkylation–dehydration–catalytic reduction) earlier in the discussion. The alcohol 1-phenylindanol, prepared by the phenylation of 1-indanone using a Grignard reagent, was dehydrated by distillation from $KHSO_4$, and the resulting olefin 1-phenylindene was hydrogenated over Raney nickel. See Pl. A. Plattner, R. Sandrin, and J. Wyss, *Helv. Chim. Acta*, **29**, 1604 (1946).

Alkylation–Reduction of Carbonyl Systems. III. The Selective Synthesis of Aromatic Hydrocarbons and Alcohols by the Alkylation–Reduction of Benzylidene Carbonyl Compounds

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Lithium–ammonia reduction of benzylidene benzyl alkoxides, generated *in situ* by alkylation of benzylidene ketones and aldehydes, yields aromatic hydrocarbons when quenched with ammonium chloride and alcohols when quenched with sodium benzoate. The following examples are cited. Phenylation–reduction of benzylidene acetophenone yields 1,1,3-triphenylpropane and 1,1,3-triphenylpropanol, respectively; benzylidene acetone yields 1,3-diphenylbutane and 1,3-diphenyl-3-butanol, respectively; benzylidene propanal yields 1,3-diphenyl-2-methylpropane and 1,3-diphenyl-2-methylpropanol, respectively; benzylidene acetaldehyde yields 1,3-diphenylpropane and 1,3-diphenylpropanol, respectively. Methylation–reduction of benzylidene acetophenone yields 1,3-diphenylbutane and 1,3-diphenyl-3-butanol, respectively; and benzylidene acetone yields 1-phenyl-3-methyl-3-butanol with either quenching agent since the intermediate alkoxide is not benzylic. Mechanistic implications are discussed.

Recently we introduced the concept of tandem alkylation–reduction of aromatic carbonyl systems as a convenient method of preparing aromatic hydrocarbons by the lithium–ammonia reduction of benzyl alkoxides generated *in situ* by alkylation.[1] In addition this laboratory has demonstrated the mechanistic and selective synthetic utility of using ammonium chloride *vis-à-vis* sodium benzoate as quenching agents in metal–ammonia reductions.[2] We now wish to report our first example of the combination of these two procedures for the selective synthesis of aromatic hydrocarbons and alcohols by the alkylation–reduction of benzylidene ketones and aldehydes. It is a method which is characterized by its simplicity, selectivity, and excellent isolated yield of the desired product. In addition the mechanistic implications are obvious.

The general procedure is to generate a benzylidene benzyl alkoxide in a metal–ammonia reaction vessel[3] by the addition of the benzylidene ketone or aldehyde to the organolithium reagent in ether. Ammonia is subsequently distilled into the vessel, followed by the addition of lithium wire; and then the resulting dark-blue mixture is cautiously quenched.

The sequence is outlined in Scheme I using two examples. Alkylation of benzylideneacetophenone (1)

(1) (a) Part I: S. S. Hall and S. D. Lipsky, *J. Chem. Soc., Chem. Commun.*, 1242 (1971). (b) Part II: S. S. Hall and S. D. Lipsky, *J. Org. Chem.*, **38**, 1735 (1973). (c) S. S. Hall and S. D. Lipsky, submitted for publication in "Organic Syntheses."

(2) (a) S. S. Hall, S. D. Lipsky, and G. H. Small, *Tetrahedron Lett.*, 1853 (1971); (b) S. S. Hall, S. D. Lipsky, F. J. McEnroe, and A. P. Bartels, *J. Org. Chem.*, **36**, 2588 (1971).

(3) For a useful general discussion of metal–ammonia experimental techniques see R. L. Augustine, Ed., "Reduction," Marcel Dekker, New York, N. Y., 1968, pp 98–105.

SCHEME I

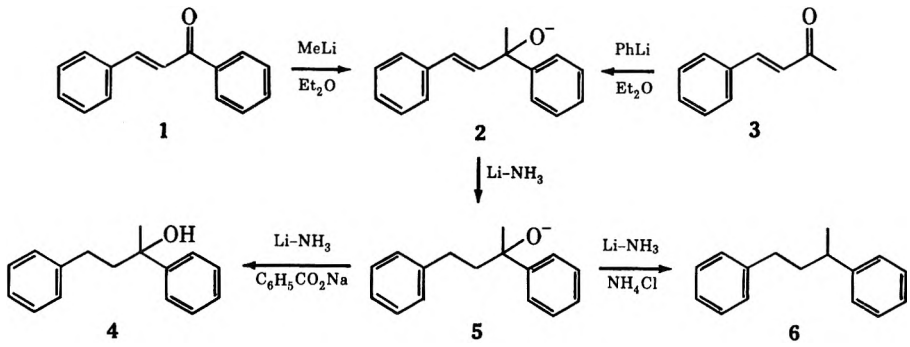
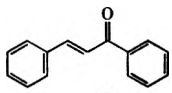
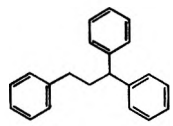
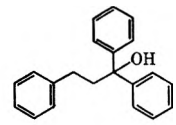
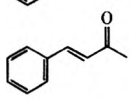
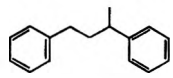
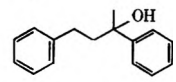
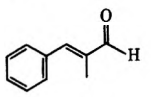
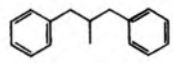
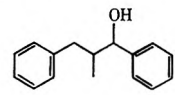
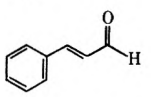
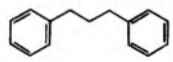
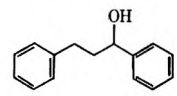
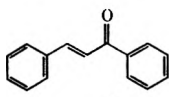
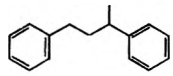
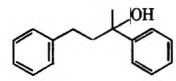
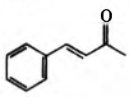
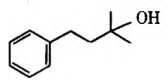
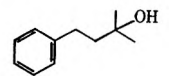


TABLE I

ALKYLATION–REDUCTION OF BENZYLIDENE CARBONYL COMPOUNDS[a]

Carbonyl compound	Registry no.	Organolithium reagent	Product: Quenching agent NH_4Cl	Registry no.	% yield anal.[b]/isol.[c]	Product: Quenching agent $C_6H_5CO_2Na$	Registry no.	% yield anal.[d]/isol.[e]
	94-41-7	C_6H_5Li		19120-39-9	100/96		6880-25-7	100/87
	122-57-6	C_6H_5Li		1520-44-1	97/84		19332-07-1	100/97
	109-39-3	C_6H_5Li		1520-46-3	99/98		38857-84-0	99/96
	104-55-2	C_6H_5Li		1081-75-0	91/77		14097-24-6	99/91
		CH_3Li		1520-44-1	99/89		6880-25-7	100/98
		CH_3Li		103-05-9	98/96			100/98

[a] Reaction conditions are those discussed in the Experimental Section. [b] Analyzed by glpc using a 6 ft × 0.25 in. 10% Apiezon L on 60–80 Chromosorb W (AW, DMCS) stainless steel column on a flame-detector instrument at a 40-ml/min flow rate. [c] Column chromatography on neutral aluminum oxide (activity I) and eluted with petroleum ether. [d] Analyzed by glpc using a 4 ft × 6 mm 4% silicone gum rubber UCC-W-982 (methylvinyl) on 80–100 HP Chromosorb W (AW, DMCS) all-glass column on a flame-detector instrument at a 40-ml/min flow rate. [e] Column chromatography on neutral aluminum oxide (activity III) and eluted with petroleum ether, petroleum ether–Et_2O.

with methyllithium or benzylideneacetone (**3**) with phenyllithium generates the benzylidene benzyl alkoxide **2**, which in the presence of lithium–ammonia is evidently reduced to the benzyl alkoxide **5**, since quenching the reaction mixture with sodium benzoate yields 1,3-diphenyl-3-butanol (**4**) quantitatively.[4] In contrast, the use of ammonium chloride as the quenching agent yields 1,3-diphenylbutane (**6**).

These results imply that at the time of quench the benzyl alkoxide **5** is present in the reaction mixture, since it has been demonstrated that benzyl alkoxides yield similar results when subjected to these conditions.[1,2] The use of sodium benzoate, a procedure introduced by this group which destroys the excess reducing agent in the absence of an external proton source, protects a benzyl alkoxide intermediate, whereas ammonium chloride protonates the benzyl alkoxide and the resulting benzyl alcohol is rapidly reduced to the aromatic hydrocarbon before all the lithium is destroyed.

The results of this study, which are summarized in Table I, indicate the selectivity and synthetic utility of this simple procedure. It also has the advantages that the benzylidene ketones and aldehydes, if not commercially available, can be readily prepared by the Claisen–Schmidt reaction or related aldol condensations;[5] and the organolithium reagents when not available can be generated *in situ* and yield similar results.

The methylation–reduction of benzylideneacetone, the last entry in Table I, is included because it represents a limitation of the procedure which is a direct consequence of the sequence of events. Lithium–ammonia reduction of the intermediate benzylidene

(4) This can be viewed as the metal–ammonia reduction of a styrene which is known to reduce to the aromatic hydrocarbon in the absence of an added proton source. See (a) ref 3, pp 118–119; (b) H. Smith, "Organic Reactions in Liquid Ammonia. Chemistry in Nonaqueous Ionizing Solvents," Vol. I, Part 2, Wiley, New York, N. Y., 1963, p 228.

(5) A. T. Nielsen and W. J. Houlihan in "Organic Reactions," Vol. 16, A. C. Cope, Ed., Wiley, New York, N. Y., 1968, pp 1–438.

alkoxide forms an alkoxide which is not benzylic and consequently cannot be reduced further during the ammonium chloride quench.[6] Hence the same product is formed using either quenching agent.

Experimental Section[7]

Alkylation–Reduction General Comments.—The entire reaction sequence was performed under a prepurified nitrogen atmosphere which is connected by a T tube to the assembly and an oil bubbler. All glassware was oven-dried, cooled to room temperature in a large box desiccator, and then quickly assembled. Phenyllithium (19.7% in ether–benzene) and methyllithium (5.1% in ether) were obtained from Foote Mineral Co. Phenyllithium was also generated *in situ* in the reaction vessel from bromobenzene and lithium foil in Et_2O. Anhydrous Et_2O was used directly from freshly opened containers. Anhydrous ammonia was distilled into the reaction vessel. Lithium wire (0.125 in., 0.01% Na, Ventron Corp.) was wiped free of oil and rinsed in petroleum ether just prior to use. All aromatic hydrocarbon and alcohol products gave satisfactory spectral and analytical data, and in some cases were compared with authentic samples. The methylation–reduction of benzylideneacetophenone (1) is described to illustrate the general procedure.

Methylation–Reduction of Benzylideneacetophenone (1).—To a solution of 7.4 mmol of MeLi in 15 ml of Et_2O in a metal–ammonia reaction vessel[3] was added, dropwise and with stirring, 1.03 g (4.95 mmol) of benzylideneacetophenone (1) in 5 ml of Et_2O. After 1 hr *ca.* 20 ml of ammonia was carefully, to prevent excessive splattering, distilled into the mixture; this was then followed by the rapid addition of 175 mg (25 mg-atoms, eight pieces) of lithium wire. The mixture soon turned dark blue with red fringes.[8]

1,3-Diphenylbutane (6, Ammonium Chloride Quench).—To the dark-blue mixture (red fringes) was cautiously added,[9] with vigorous stirring, *ca.* 3 g of ammonium chloride until the mixture turned white (*ca.* 4 min) and the ammonia was allowed to evaporate. After the residue had been partitioned between aqueous NaCl and Et_2O, the organic phase was dried ($MgSO_4$), filtered, concentrated at water aspirator pressure at 40–50°, and analyzed (glpc). Following chromatography (neutral aluminum oxide, activity I; petroleum ether) 0.925 g (89%) of 1,3-diphenylbutane (6) was obtained as a colorless liquid: ir (film) 3080, 3060, 3030, 1600, 1495, 700 (aromatic); 2960, 2930, 2860, 1450, 1375 cm^{-1} (CH_3, CH_2, CH); nmr (CCl_4, TMS) δ 1.22 (3 H, d, J = 7 Hz, CH_3), 1.6–2.1 (2 H, m, CH_2), 2.5 (2 H, t, J = 8 Hz, CH_2), 2.6 (1 H, apparent sextet, J = 7 Hz, CH), and apparent singlets at 7.14 (4 H, Ar) and 7.2 (6 H, Ar); mass spectrum m/e (rel intensity) 210 (M^+, 14), 119 (11), 105 (100), 91 (61), and 77 (22).

Anal. Calcd for $C_{16}H_{18}$: C, 91.37; H, 8.63. Found: C, 91.39; H, 8.61.

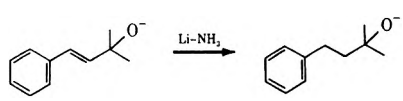
This product was identical with that obtained by the phenylation–reduction (ammonium chloride quench) of benzylideneacetone (3).

1,3-Diphenyl-3-butanol (4, Sodium Benzoate Quench).—To the dark-blue mixture (red fringes) was cautiously added,[9] with vigorous stirring, *ca.* 1.5 g of sodium benzoate until the mixture turned yellow (*ca.* 4 min) and then the ammonia was allowed to evaporate. Normal work-up (described above) and chromatography (neutral aluminum oxide, activity III; petroleum ether, petroleum ether–Et_2O) yielded 1.1 g (98%) of 1,3-diphenyl-3-butanol (4) obtained as a pale-yellow syrup exhibiting the following spectral properties: ir (film) spectrum was almost superimposable on that from product 6 except for additional bands at 3560, 3410 (broad), and 1120 cm^{-1}; nmr (CCl_4, TMS) δ 1.48 (3 H, s, CH_3), 1.7–2.1 (2 H, m, CH_2), a broad singlet, disappears when D_2O is added, at 2.4 (1 H, –OH) which is superimposed on a multiplet at 2.2–2.7 (2 H, CH_2), and a complex pattern at 6.8–7.4 (10 H, Ar); mass spectrum m/e (rel intensity) 226 (M^+, 1), 211 (2), 209 (4), 208 (13), 193 (11), 121 (100), 107 (41), 106 (25), 105 (24), 91 (73), 77 (35), and 43 (99).

Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.72; H, 8.09.

This product was identical with that obtained by the phenylation–reduction (sodium benzoate quench) of benzylideneacetone (3).

Acknowledgment.—The author wishes to thank Ms. Rose Marie Luethy and Mr. Paul P. Vallon, Givaudan Corp., Clifton, N. J., for the mass spectra, and Dr. Franz J. Scheidl, Hoffmann-La Roche Inc., Nutley, N. J., for the microanalyses.

(6) 

(7) Spectral measurements were determined with the following instruments: ir, Perkin-Elmer Model 237; nmr, Varian Associates Model A-60; mass spectra, Perkin-Elmer Model 270 with a Varian Associates Model 620/i computer attachment. Gas chromatographic analyses (glpc) of the aromatic hydrocarbons (ammonium chloride quench) were performed on a Hewlett-Packard Model 5750 research chromatograph (flame detector) using a 6 ft × 0.25 in. (stainless steel) 10% Apiezon L on 60–80 Chromosorb W (AW, DMCS) column and the benzyl alcohols (sodium benzoate quench) on a Hewlett-Packard Model 7610 high-efficiency chromatograph (flame detector) using a 4 ft × 6 mm (all glass) 4% silicone gum rubber UCC-W-982 (methylvinyl) on 80–100 HP Chromosorb W (AW, DMCS) column. Column chromatography of the aromatic hydrocarbons was performed on neutral aluminum oxide (activity I) using petroleum ether (bp 33–58°) and chromatography of the alcohols was performed on neutral aluminum oxide (activity III) using petroleum ether and petroleum ether–Et_2O.

(8) Normally *ca.* 20 min elapsed before proceeding with the quenching step, although the time interval does not seem too critical.

(9) The quenching agent was most conveniently introduced by attaching a glass tube filled with the salt to a side arm with tygon tubing. When the quenching agent is to be added the tube is raised and tapped gently to smoothly introduce the salt. Should this step start to become violent, the addition and the vigorous stirring should be momentarily halted to avoid an eruption.

Notes

Oxidative Substitution on Halophenols

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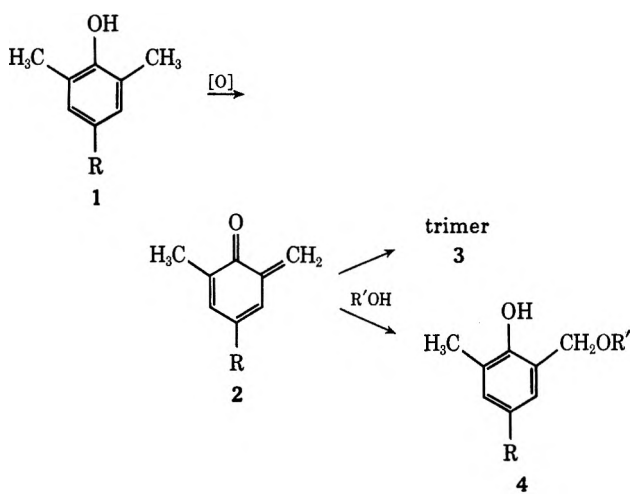
Organic acids or phenols replace the halogen in 4-halogen substituted phenols when one-electron oxidizing agents oxidize the substituted phenol in the presence of the acid or phenol. Such a reaction allows the synthesis of a variety of substituted phenols, under mild conditions, which are difficult to make by other means.

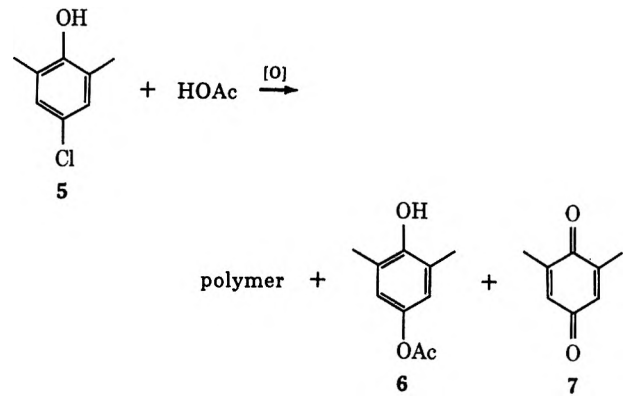
Hunter[1,2] and Price[3] observed halogen replacement reactions in the oxidation of 4-bromo-2,6-xylenol to polyphenylene oxide with concurrent loss of halogen. More highly halogen substituted phenols such as pentachlorophenol, when oxidized, yield quinol ethers, with no loss of halogen, instead of polymers.[4,5] In certain cases the coupling occurs with carbon–carbon bond formation (diphenoquinones) rather than with carbon–oxygen bond formation as in quinol ethers.[6] These couplings are free-radical dimerizations.

One-electron oxidation of phenols without 4-halogen substitutents, particularly 4-substituted 2,6-xylenol (**1**), can give an *o*-quinone methide **2** which can react with itself to give a trimer **3** or with another hydroxyl-containing group to give a benzyl ether **4**.[7,8] When R



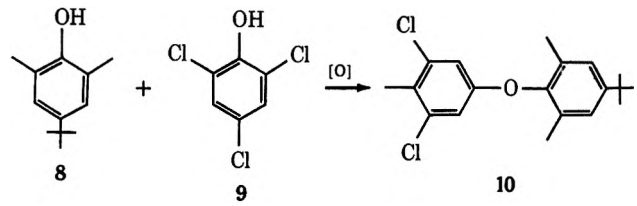
is a halogen this sequence is not followed. No trimer or benzyl ether is found; the observed products result from substitution of the halogen by some other group.

When 4-chloro-2,6-xylenol (**5**) is oxidized with either silver oxide or potassium permanganate in acetic acid, two products are formed in addition to the expected polymer. The material present in larger amount was identified as 4-acetoxy-2,6-xylenol by comparison of its mass spectrum, infrared spectrum, and retention time of its trimethylsilyl ether[9] with those of authentic **6**.[10] The second material is 2,6-xyloquinone (**7**).



A similar substitution is obtained with benzoic acid where dimethylformamide is needed as a solvent. This oxidation yields 4-benzoyloxy-2,6-xylenol when 4-chloro-2,6-xylenol is oxidized with silver oxide.

In addition to organic acids, phenols will replace the halogen on a chlorophenol. The oxidation with silver oxide of a mixture of 4-*tert*-butyl-2,6-xylenol (**8**) and

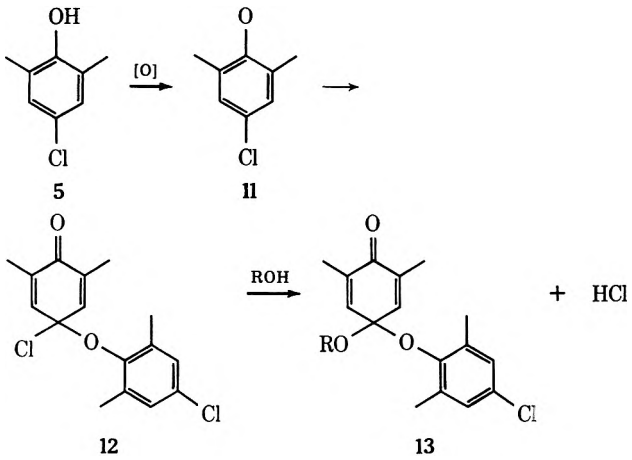


2,4,6-trichlorophenol (**9**) in a 1:1 ratio gives the phenoxy phenol **10** as the chief product. An nmr and mass spectrum identified **10** as the illustrated para isomer.

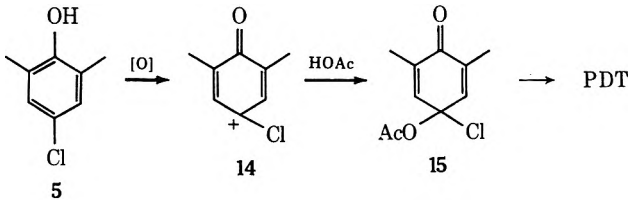
These reactions probably all occur by a similar mechanism. One mechanism that accounts for these results involves oxidation of **5** to the radical **11**, which then dimerizes to the quinol ether **12**, a well-known reaction. This intermediate solvolyzes, perhaps by some sort of ionic reaction, with the attendant organic acid or phenol to yield the quinone ketal **13**, which can then separate and abstract a hydrogen to yield 4-acetoxy-2,6-xylenol (R = AcO) or solvolyze to 2,6-xyloquinone.

Although this work uses typical one-electron oxidizing agents, there appears to be mounting evidence that in certain cases the two electrons can be removed with equal ease.[11] If this should occur in these reactions,

(1) W. H. Hunter and A. A. Levine, *J. Amer. Chem. Soc.*, **48**, 1608 (1926).
(2) W. H. Hunter and M. Morse, *J. Amer. Chem. Soc.*, **48**, 1615 (1926).
(3) G. Staffin and C. C. Price, *J. Amer. Chem. Soc.*, **82**, 3632 (1960).
(4) E. Muller, A. Rieker, and W. Beckert, *Z. Naturforsch. B*, **17**, 567 (1962).
(5) H. D. Becker, *J. Org. Chem.*, **29**, 3068 (1964).
(6) C. J. R. Adderley and F. R. Hewgill, *J. Chem. Soc. C*, 2770 (1968), and earlier papers.
(7) D. A. Bolon, *J. Org. Chem.*, **35**, 715 (1970).
(8) D. A. Bolon, *J. Org. Chem.*, **35**, 3666 (1970).
(9) J. F. Klebe, H. Finkbeiner, and D. M. White, *J. Amer. Chem. Soc.*, **88**, 3390 (1966).
(10) E. Zbiral, F. Wessely, and E. Lahrmann, *Monatsh. Chem.*, **91**, 331 (1960).
(11) M. Chanham, F. M. Dean, K. Kindley, and M. Robinson, *J. Chem. Soc. D*, **19**, 1141 (1971).



the phenol **5** could be oxidized directly to **14** and subsequently yield the products by a solvolysis mechanism.



In all of the reactions a polymeric material forms which is probably a polyphenylene oxide polymer but which was not characterized.

This reaction offers a method of making some substituted phenols which would be difficult to make by other means. The conditions are mild and the reaction easy to run.

The reaction is general in the sense that a wide variety of oxidants yield identical results. Lead dioxide, silver oxide, and potassium permanganate all give the same distribution of products. Phenols that fulfill the conditions of blocked ortho positions also will work. Alcohols do not give a similar product distribution and an investigation of this reaction is under way.

Experimental Section

4-Chloro-2,6-xylenol and 2,4,6-Trichlorophenol.—These materails were used as obtained from Aldrich Chemical Co.

4-*tert*-Butyl-2,6-xylenol.—This material was prepared by butylation of 2,6-xylenol.[7]

Oxidation of 4-Chloro-2,6-xylenol (5) in Acetic Acid.—The slow addition of powdered potassium permanganate (1.58 g, 0.05 equiv) to 4-chloro-2,6-xylenol (2.34 g, 0.015 mol) in glacial acetic acid (75 ml) produced a bright yellow solution which was poured into water and the organics were extracted with ether. The ether was washed with sodium bicarbonate solution and water and dried, and the ether was distilled, which left a yellow gum. Upon treatment with bis(trimethylsilyl)acetamide[9] the sample became sufficiently volatile so that it could be analyzed by vapor phase chromatography (vpc) and the major product was collected. This material is 4-acetoxy-2,6-xylenol trimethylsilyl ether, as shown by mass spectra (molecular weight and fragmentation pattern), infrared spectrum, and vpc retention time when compared with those of an authentic material.[12]

The residual oil gave pale yellow crystals (0.4 g, 8%) when dissolved in hexane and cooled to −20°. These crystals, mp 65–67°, are 2,6-xyloquinone, as shown by the mixture melting point and a comparison of infrared spectra with those of an authentic material.[6]

Oxidation of 4-Chloro-2,6-xylenol and Benzoic Acid.—Silver oxide (6.96 g, 0.03 mol) was stirred with a mixture of 4-chloro-2,6-xylenol (4.68 g, 0.03 mol), benzoic acid (3.66 g, 0.03 mol), magnesium sulfate, and dimethylformamide over an 18-hr period. The solid silver salts were filtered and the filtrate was placed in water. Ether extraction removed the organic materials, after which sodium bicarbonate and water washes removed contaminants. The dried ether was distilled, leaving a red, gummy residue. The gum was dissolved in hexane and cooled to −20°. Tan crystals formed in a yield of 12%. Recrystallization of these crystals gave a yellow solid which was 4-benzoyloxy-2,6-xylenol, mp 139–141°. The infrared spectrum shows a hydroxyl at 3430, carbonyl at 1725, and phenyl absorbtions at 710 and 735 cm^{-1} which support the assigned structure **6** (OAc = OBz).

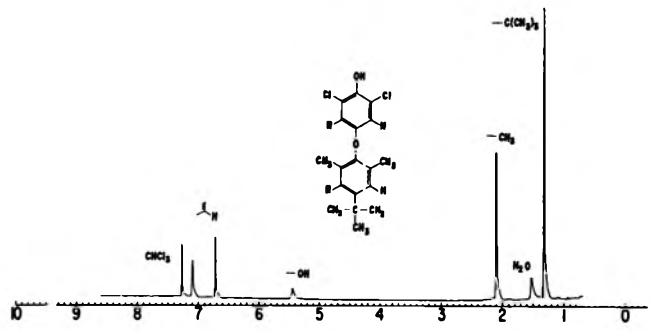


Figure 1.

Anal. Calcd for $C_6H_{14}O_3$: C, 74.4; H, 5.8; mol wt, 242. Found: C, 74.5; H, 5.7; mol wt, 245.

Oxidation of 4-*tert*-Butyl-2,6-xylenol and 2,4,6-Trichlorophenol.—4-*tert*-Butyl-2,6-xylenol (1.78 g, 0.01 mol) and 2,4,6-trichlorophenol (1.97 g, 0.01 mol) in benzene were stirred with silver oxide (2.3 g, 0.01 mol) for 0.5 hr and then filtered. A vpc of the silylated reaction mixture showed that the products were 80% phenoxy phenol **10** and 20% mixed monomers. A sample of silylated **10** was collected from the vpc and gave the correct mass spectrum for the trimethylsilyl derivative of **10**; major peaks at *m/e* 412, 410, and 177 (phenoxy) were found along with no evidence for three chlorines on the molecule.

Chromatography of the residue after filtration and benzene removal, and elution by hexane followed by 20% benzene–hexane, gave several fractions. One consisted of 0.16 g of solids which a vpc analysis showed was 90% **10**. This fraction, when separated by preparative thin layer chromatography, gave 0.102 g of a gum which crystallized at −30°, giving white plates, mp 105–106°.

Anal. Calcd as $C_{18}H_{20}O_2Cl_2$: C, 63.7; H, 5.9. Found: C, 63.7; H, 6.2.

The nmr spectrum of this material (Figure 1) clearly shows that the structure of **10** is the assigned 4 isomer.

Registry No.—**5**, 1123-63-3; **6** trimethylsilyl ether, 38645-01-1; **8**, 879-97-0; **9**, 88-06-2; **10**, 38645-02-2; 4-benzoyloxy-2,6-xylenol, 38645-03-3.

(12) H. Finkbeiner and A. Toothaker, *J. Org. Chem.*, **33**, 4347 (1968).

The Mechanism of the Cope Elimination

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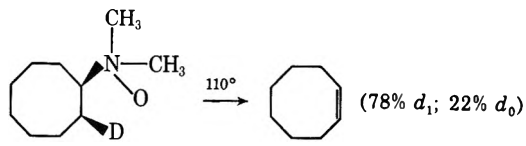
The Cope elimination[1] involves the thermal decomposition of an amine oxide by a five-membered cyclic transition state. This reaction has been extensively used as a "reference reaction" for syn elimination, since its mechanism has been considered to be essentially

(1) A. C. Cope and E. R. Trumbull, *Org. React.*, **11**, 317 (1960).

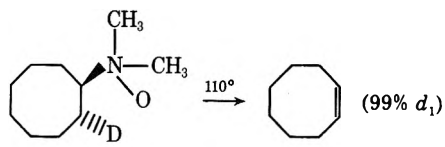
beyond doubt.[2] Although there is good evidence[1,3] that the pyrolysis of an amine oxide involves syn-elimination, this mechanism has never been rigorously tested by deuterium-labeling experiments. Since considerable emphasis has been placed on this reaction we now report unequivocal deuterium-labeling evidence that establishes the mechanism of the Cope elimination as a 100% syn elimination.

The specifically labeled *N,N*-dimethylcyclooctylamines were prepared according to the method of Coke.[4] The amine oxides were prepared by oxidation of the labeled tertiary amines with 36% hydrogen peroxide affording *cis*- and *trans*-*N,N*-dimethylcyclooctyl oxide-2-d_1. Pyrolysis of the cis-2-d_1 oxide **1** at 110° (11 mm) afforded *cis*-cyclooctene that had retained 78% of its initial deuterium content (Scheme I).

SCHEME I



1



2

From these data a syn k_H/k_D of 3.5 may be calculated. The deuterium content was analyzed by mass spectrometry on a sample purified by gas chromatography. Pyrolysis of the trans-2-d_1 oxide 2 afforded *cis*-cyclooctene that had retained 100% (within experimental error) of the deuterium initially present in the amine oxide, providing unequivical evidence for an exclusive syn elimination.

The complete absence of *trans*-cyclooctene (gc analysis) in the pyrolyses of **1** and **2** is worthy of comment. The stereoselective formation of cis olefin has been taken[3a,5] as evidence for the intramolecular cyclic mechanism, because the atoms eliminated would be in a preferred planar transition state. This reaction may be considered an analog of the ylide mechanism in which an α' oxy anion rather than the carbanion basic center is involved. We recently reported[6] that *trans*-cyclooctene can be readily formed by an α',β elimination in liquid ammonia using KNH_2 as the base (syn k_H/k_D = 5.89). Thus, a cyclic intramolecular transition state to form the more strained (~9 kcal/mol relative to the cis isomer) trans olefin is not precluded in the cyclooctyl system. Therefore the cis/trans ratio observed in these reactions should not be used as an indication of the mechanism involved.[7] As an alternate explanation we suggest that the exclusive formation of *cis*-cyclooctene is a manifestation of the weakly basic oxy anion. In the Cope elimination both C–H and C–N bond cleavage may be well advanced at the transition state with considerable development of double-bond character. However, with the strongly basic nitrogen ylide[6] there might be more C–H cleavage than C–N cleavage in the transition state. In support of this suggestion, stabilized benzyl ylides[7] and sulfonium ylides[8] also afford the thermodynamically favored cis olefin. Thus, in the present case product development control results in exclusive formation of the cis stereoisomer.

(2) J. Zavada, J. Krupicka, and J. Sicher, *Collect. Czech. Chem. Commun.*, **31**, 4273 (1966); J. Sicher, *Angew. Chem., Int. Ed. Engl.*, **11**, 200 (1972).

(3) (a) C. H. DePuy and R. W. King, *Chem. Rev.*, **60**, 431 (1960); (b) M. R. V. Sahyun and D. J. Cram, *J. Amer. Chem. Soc.*, **85**, 1263 (1963).

(4) J. L. Coke and M. C. Mourning, *J. Amer. Chem. Soc.*, **90**, 5561 (1968).

(5) A. C. Cope, R. A. Pike, and C. F. Spencer, *J. Amer. Chem. Soc.*, **75**, 3213 (1953).

(6) (a) R. D. Bach and D. Andrzejewski, *J. Amer. Chem. Soc.*, **93**, 7118 (1971); (b) R. D. Bach, K. W. Bair, and D. Andrzejewski, *ibid.*, **94**, 8608 (1972).

(7) G. Wittig and R. Polster, *Justus Liebigs Ann. Chem.*, **612**, 102 (1958); C. L. Bumgardner, *J. Org. Chem.*, **27**, 1035 (1962).

Experimental Section

Mass spectral analyses were performed on an MS-902 mass spectrometer. *cis*-Cyclooctene and *N,N*-dimethylcyclooctylamine were purified by preparative gas chromatography and analyzed at 11 eV. The deuterium analyses were corrected for 83.3% and the 86.7% isotopic purity of the starting compounds, *N,N*-dimethyl-*cis*- and *N,N*-dimethyl-*trans*-cyclooctylamine-2-d_1. The *cis*-cyclooctene and the labeled amines were collected on a 6-ft 10% SE-30 column at 150° prior to mass spectral analysis. Gas chromatographic analyses of the reaction mixtures were carried out with a 6-ft 10% NMPN column at 80°.

The *cis*-cyclooctene was obtained as a gift from Columbian Carbon Co. *trans*-Cyclooctene was prepared as reported previously.[9] *cis*- and *trans*-cyclooctene were converted to *cis*- and *trans*-cyclooctylamine-2-d_1, bp 80–81° (20 mm), according to the procedure of Coke and Mourning.[4] The Clark–Eschweiler procedure described by Icke[4,10] was used to prepare the specifically labeled *N,N*-dimethylcyclooctylamines.

***N,N*-Dimethyl-*cis*-cyclooctylamine-2-d_1 Oxide.**—To a stirring solution of 1 ml of reagent methanol was added 0.028 g (0.180 mmol) of *N,N*-dimethyl-*cis*-cyclooctylamine-2-d_1[4] and 30 μl (1.3 mmol) of 36% hydrogen peroxide. After 3 days at room temperature the solvent was removed by rotary evaporation, affording the crude amine oxide as a viscous oil.

***N,N*-Dimethyl-*trans*-cyclooctylamine-2-d_1 Oxide.**—The above procedure was repeated on 0.028 g of *N,N*-dimethyl-*trans*-cyclooctylamine-2-d_1 affording the trans labeled amine oxide as a viscous oil.

Cope Elimination.—The crude amine oxides were heated at 110° (11 mm) and the temperature was slowly raised to 120° over a 30-min period. The pyrolysis products were collected in a cold trap in a pentane solution and washed with 10% HCl. The *cis*-cyclooctene was isolated by preparative gas chromatography. The product composition was at least 99.9% *cis*-cyclooctene with none of the trans isomer being observed by gc analysis.

Registry No.—**1**, 38645-04-4; **2**, 38645-05-5.

Acknowledgment.—We wish to express our appreciation to donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research.

(8) V. Franzen and H. J. Schmidt, *Chem. Ber.*, **94**, 2937 (1961).

(9) A. C. Cope and R. D. Bach, *Org. Syn.*, **49**, 39 (1969).

(10) R. N. Icke, B. B. Wisegarver, and G. A. Alles, "Organic Syntheses," Collect. Vol. III, E. C. Hornung, Ed., Wiley, New York, N. Y., 1955, p 723.

The Synthesis of Hycanthone

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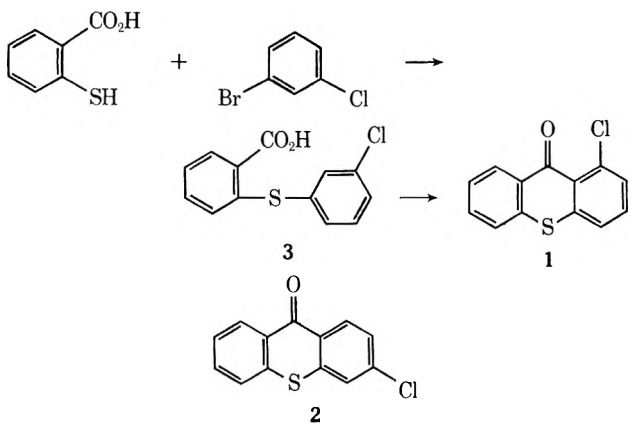
Hycanthone (**7**), a schistosomicidal agent, was first prepared by Rosi, *et al.*, by microbiological oxidation of the corresponding 4-methylthioxanthenone,

lucanthone.[1-3] We now wish to report a chemical synthesis of hycanthone from 1-chlorothioxanthen-9-one (**1**). Although Mahishi, *et al.*,[4] claim to have prepared pure **1** by cyclization of *o*-[(*m*-chlorophenyl)-thio]benzoic acid (**3**) (Scheme I), we found that the

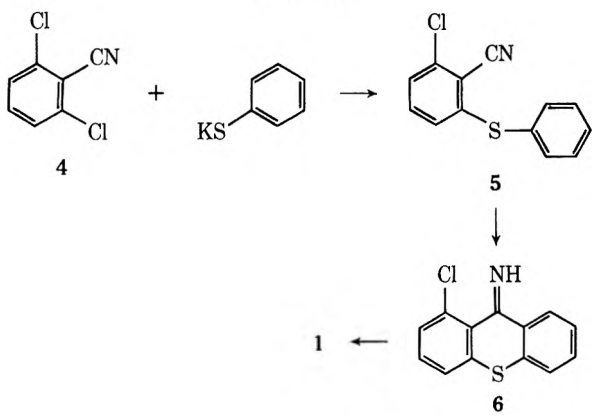
SCHEME I



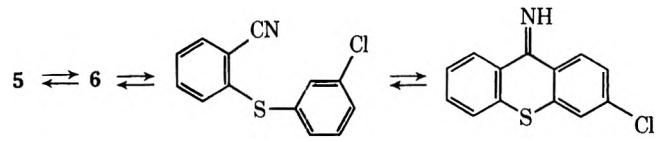
product was an approximately 50:50 mixture of **1** and 3-chlorothioxanthen-9-one (**2**).[5,5a]

We, therefore, prepared **1** by an alternate route (Scheme II) which was designed to afford pure **1**.

SCHEME II



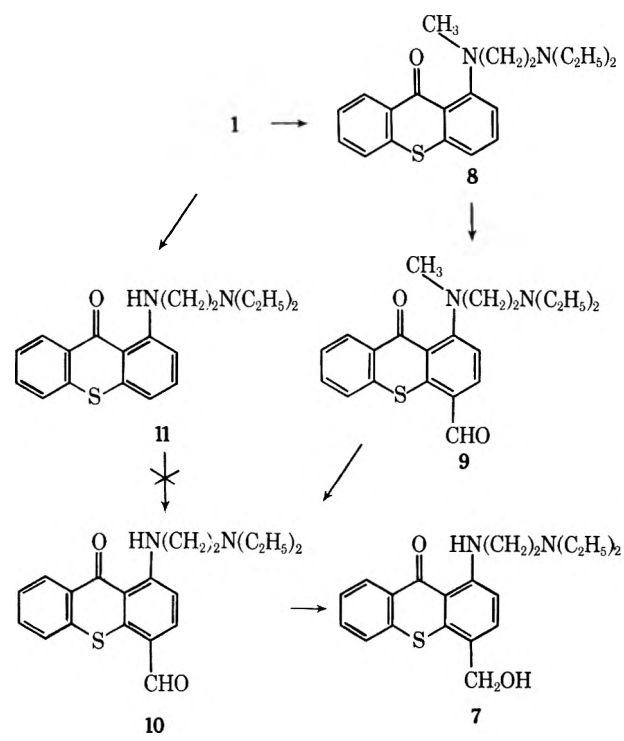
2-Chloro-6-(phenylthio)benzonitrile (**5**) was easily prepared from 2,6-dichlorobenzonitrile (**4**) and potassium thiophenolate in DMSO. A similar preparation of **5** has been reported utilizing 2-chloro-6-nitrobenzonitrile in place of **4**.[6] The nitrile **5** was cyclized in polyphosphoric acid and the imine intermediate **6** was hydrolyzed in water to give a 66% yield of the desired chloro compound **1**. Optimum yields of **1** were obtained when the PPA cyclization was carried out at 150–170°. As the cyclization temperature was raised above this range, increasing amounts of the 3-chloro isomer **2** formed and at 260° **2** was the sole product produced. The formation of **2** is presumably a result of the following temperature-dependent reactions.



An attempt was made to prepare 2-chloro-6-(phenylthio)benzoic acid from 2,6-dichlorobenzoic acid and thiophenol. Unreacted acid was recovered when the reaction was run in refluxing DMF. When this same reaction was run with a copper catalyst present (Ullmann conditions), no acidic procduts were obtained and gas chromatography revealed the presence of *m*-dichlorobenzene, indicating that decarboxylation had occurred. In an attempt to block this decarboxylation the reaction was run with methyl 2,6-dichlorobenzoate in place of the corresponding acid. Although none of the desired sulfide formed, gas chromatography indicated the presence of thioanisole. The ester apparently behaved as an alkylating agent to form thioanisole and 2,6-dichlorobenzoic acid.[7]

The synthesis of hycanthone (**7**) from **1** is shown in Scheme III.

SCHEME III



Compound **8** was prepared by treating **1** with *N*,*N*-diethyl-*N'*-methylethylenediamine in refluxing pyridine. This same reaction can be run on the mixture of 1- and 3-chlorothioxanthen-9-ones, obtained from cyclization of **3**, since the 3 isomer **2** is unreactive in refluxing pyridine. The chlorine atom of **2** can, however, be displaced in refluxing DMF. Reaction of **8** with phosphorus oxychloride in DMF (Vilsmeier conditions)

(1) D. Rosi, G. Peruzzotti, E. W. Dennis, D. A. Berberian, H. Freele, and S. Archer, *Nature (London)*, **208**, 1005 (1965).

(2) H. Mauss, *Ber.*, **81**, 19 (1948).

(3) D. Rosi, G. Peruzzotti, E. W. Dennis, D. A. Berberian, H. Freele, B. F. Tullar, and S. Archer, *J. Med. Chem.*, **10**, 867 (1967).

(4) N. B. Mahishi, P. B. Sattur, and K. S. Nargund, *J. Karnatak Univ.*, **2** (1), 50 (1957); *Chem. Abstr.*, **53**, 14101 (1959).

(5) A recent patent reports the preparation of the isomeric 3-chlorothioxanthen-9-one by essentially the same procedure employed by Mahishi, *et al.*: British Patent 1,000,509 (1965); *Chem. Abstr.*, **58**, 12518*f* (1963).

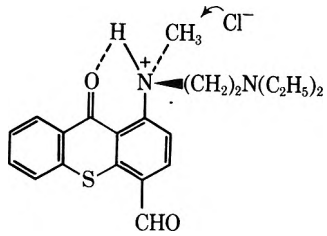
(5a) NOTE ADDED IN PROOF.—A recent paper reports essentially the same mixture of **1** and **2** obtained by us by cyclization of **3** in strong acid. These authors also describe an unambiguous synthesis of **1** starting with 6-chloroanthranilic acid: I. Okabayashi, *et al.*, *Yakugaka Zasshi*, **92**, 1386 (1972).

(6) British Patent 951,651 (1964); *Chem. Abstr.*, **61**, P5575*b* (1964).

(7) A similar hydrolysis was reported recently: P. A. Bartlett and W. S. Johnson, *Tetrahedron Lett.*, 4459 (1970).

afforded the aldehyde **9** with no evidence of formylation in the 2 position of the thioxanthene ring. A similar Vilsmeier reaction on **11** did not yield the desired aldehyde **10**. The *N*-methyl group of **8** functions, therefore, as a protecting group allowing formylation in the 4 position. The methyl group of **9** was then removed with pyridine hydrochloride to yield compound **10**, which has been reported previously as a by-product in the microbiological oxidation of lucanthone.[3] Sodium borohydride reduction of **10** afforded hycanthone[8] in 15% overall yield from pure **1**.

The demethylation of **9** presumably proceeds in the following manner.



The peri oxygen atom may stabilize this intermediate through hydrogen bonding. Attack of the chloride ion on the methyl group then yields **10**. There was no evidence of N-dealkylation of the other, more hindered, alkyl group.

Experimental Section

All melting points are corrected. Thin layer chromatograms were developed on precoated silica gel F-254 Merck plates. Gas chromatograms were recorded on a Hewlett-Packard Model 5750 gas chromatograph. The ir spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer and the nmr spectra were determined on a Varian Model A-60 or a Varian HA-100 spectrometer.

Elemental analyses were performed by Istranal Laboratories, Rensselaer, N. Y., or Galbraith Laboratories, Inc., Knoxville, Tenn.

2-Chloro-6-(phenylthio)benzonitrile (5).—Thiophenol (13 ml, 0.15 mol) in DMSO (50 ml) was dripped into a cooled suspension of potassium *tert*-butoxide (13.0 g, 0.15 mol) in DMSO (300 ml). 2,6-Dichlorobenzonitrile (19.0 g, 0.11 mol) in DMSO (300 ml) was added dropwise to this mixture with stirring over a 30-min period. The reaction mixture was heated on a steam bath for 2.5 hr and then poured into cold H_2O (1 l.) and allowed to stand while the oily product solidified. Recrystallization from ethanol (125 ml) yielded white prisms, 19.5 g (72%), mp 67–72° (lit.[6] mp 66–67°).

1-Chlorothioxanthen-9-one (1).—Compound **5** (25 g, 0.10 mol) was suspended in PPA (2.5 l.) and heated with vigorous stirring for 6 hr at 150–170°. The reaction mixture was allowed to cool to 90° and poured into an ice–water (12 l.) mixture with stirring. The aqueous mixture was warmed on a steam bath for several hours and cooled (ice bath), and **1** was collected by filtration (sintered glass). Recrystallization from isopropyl alcohol (125 ml) afforded **1** as pale yellow needles: 14.0 g (56%); mp 112.5–114.0° (lit.[4] mp 146°]; uv max (EtOH) 221 mμ (log ε 4.19), 258 (4.62), 293 (3.70), 303 (3.72), 380 (3.75); ir (KBr) 1638 cm^{-1} (C=O); nmr ($CDCl_3$) δ 8.40 (m, 1, peri H), 7.15–7.55 (m, 6, aromatic H).

Anal. Calcd for $C_{13}H_7ClOS$: C, 63.28; H, 2.85; Cl, 14.37; S, 12.99. Found: C, 63.28; H, 2.98; Cl, 14.39; S, 13.11.

***o*-[(*m*-Chlorophenyl)thio]benzoic Acid** (3).—Thiosalicylic acid (30 g, 0.19 mol), copper bronze (1.86 g), KI (1.75 g, 0.010 mol), and K_2CO_3 (40.5 g, 0.29 ml) were combined in DMF (450 ml). The mixture was warmed to 100° and *m*-bromochlorobenzene (40.8 g, 0.21 mol) in DMF (25 ml) was added. The reaction mixture was refluxed for 18 hr and then poured into an ice–water (1.0 l.) mixture. The aqueous mixture was charcoaled, filtered, and made acidic (3 *N* HCl). **3** was collected and recrystallized from glacial acetic acid (300 ml), 30.4 g (61%), mp 186–194° (lit.[4] mp 192–194°).

1 and 3-Chlorothioxanthen-9-one (2).—Compound **3** (16.3 g, 0.061 mol) was suspended in concentrated H_2SO_4 (50 ml) and stirred at ambient temperatures for 2 hr. The reaction mixture was poured into an ice–water mixture (300 ml) and the crude products were collected by filtration, 15.2 g (100%), mp 150–165°. Vpc analysis of this mixture showed it to be a 52:48 mixture of **1** and **2**.[9] Pure **2** was also prepared by an unambiguous synthesis.[4] A portion of the above mixture was recrystallized several times from isopropyl alcohol to yield **2**, mp 171–173° (lit.[4] mp 176°).

1-{[2-(Diethylamino)ethyl]methylamino}thioxanthen-9-one (8).—Compound **1** (5.0 g, 0.020 mol), *N*,*N*-diethyl-*N'*-methylethylenediamine (3.26 g, 0.025 mol), and pyridine (15 ml) were refluxed for 36 hr. The solvents were removed under reduced pressure and the residue was dissolved in 10% aqueous acetic acid (40.0 ml), charcoaled, filtered, and extracted with methylene dichloride (40.0 ml). The aqueous layer was made basic with 35% aqueous NaOH solution (15.0 ml) and extracted with methylene dichloride (300 ml). The organic layer was dried, filtered, and concentrated to an oil, 3.41 g (50%). This oil was converted to its dihydrochloride and recrystallized from acetonitrile: 1.10 g; mp 160.5–161.0°; uv max (EtOH) 262 mμ (log ε 4.54), 315 (3.61), 322 sh (3.60), 375 (3.42), 428 (3.56); ir ($CHCl_3$) 1605 cm^{-1} (C=O); nmr (D_2O) δ 7.65–9.00 [m, 7, aromatic H), 5.13 (s, 2, exchanged H's), 4.58 (m, 2, NCH_2), 3.87 (s, 3, NCH_3), 3.33–4.08 (m, 6, 3 NCH_2), 1.70 (t, 6, 2 NCH_3).

Anal. Calcd for $C_{20}H_{26}Cl_2N_2OS$: C, 58.10; H, 6.33; N, 6.77; S, 7.75. Found: C, 57.65; H, 6.37; N, 7.04; S, 7.63.

Compound **8** could also be prepared from a mixture of **1** and **2** using the procedure described above, partitioning the unreacted **2** and **8** between an organic layer (chloroform) and aqueous acetic acid. This also provides a useful synthesis for pure 3-chlorothioxanthen-9-one (**2**).

1-{[2-(Diethylamino)ethyl]amino}thioxanthen-9-one (11).—Compound **11** was prepared from a mixture of **1** and **2** using the general procedure outlined in the synthesis of **8**. Thus a mixture (26 g, 0.10 mol) of **1** and **2** yielded 15 g (88.5% from **1**) of **11** as yellow plates when recrystallized from ethanol, mp 83–85°, ir (KBr) 1605 cm^{-1} (C=O).

Anal. Calcd for $C_{19}H_{22}N_2OS$: C, 69.89; H, 6.79; N, 8.58. Found: C, 69.83; H, 6.84; N, 8.28.

1-{[2-(Diethylamino)ethyl]methylamino}-9-oxothioxanthene-4-carboxaldehyde (9).—Compound **8** (10 g, 0.029 mol) was dissolved in DMF (70 ml), and phosphorus oxychloride (5.5 ml, 0.06 mol) was slowly added as the temperature rose to 55°. The reaction mixture was heated on a steam bath for 1 hr, cooled, and poured into ice water (200 ml). The mixture was made basic with 35% aqueous sodium hydroxide (30 ml) and extracted with chloroform (300 ml) to yield **9** isolated as its hydrochloride: 7.4 g (63%); mp 202–204°; uv max (EtOH) 256 mμ (log ε 4.39), 272 sh (4.21), 301 (4.15), 333 (4.20), 415 (3.83); ir (KBr) 1655 cm^{-1} (HC=O), 1605 (C=O); nmr (D_2O) δ 9.30 (s, 1, CHO), 6.65–8.35 (m, 6, aromatic H), 5.18 (s, 1, exchanged H), 3.33–4.83 (m, 8, 4 NCH_2), 2.95 (s, 3, NCH_3), 1.71 (t, 6, 2 CH_3).

Anal. Calcd for $C_{21}H_{23}ClN_2O_2S$: C, 62.28; H, 6.22; N, 6.91. Found: C, 62.25; H, 6.22; N, 7.00.

1-{[2-(Diethylamino)ethyl]amino}-9-oxothioxanthene-4-carboxyaldehyde (10).—Compound **9** (5.4 g, 0.013 mol), as its hydrochloride, was heated in pyridine hydrochloride (25 g, 0.216 mol) at 140° for 1 hr and then treated with H_2O and made basic with 35% aqueous sodium hydroxide. Extraction with ether yielded **10**, which was recrystallized from isopropyl acetate (50 ml), 3.85 g (91%), mp 118–120° (lit.[3] mp 119.4–120.6°).

1-{[2-(Diethylamino)ethyl]amino}-4-(hydroxymethyl)thioxanthen-9-one, Hycanthone (7).—The aldehyde **10** (3.80 g, 12 mmol) was dissolved in methanol (50 ml) and treated with sufficient sodium borohydride at room temperature to reduce **10** to **7** as evidenced by tlc examination. (Plates were sprayed with a solution of 2,4-dinitrophenylhydrazine and the addition of sodium borohydride was terminated when no aldehyde was evident.) Methanol was removed and the residue was taken up in benzene and washed with water until the pH was 8.0. The benzene solution was dried ($MgSO_4$), filtered, and concentrated to a yellow solid which was recrystallized from isopropyl acetate (45

(8) The conversion of **10** to hycanthone has been previously described; see ref 3.

(9) All vpc analyses were run utilizing a glass column, 0.25 in. × 4 ft, and packed with 3% OV-1 as the stationary phase.

ml). Hycanthone was collected as yellow prisms: 2.71 g (71%); mp 95–98° (lit.[3] mp 101–102.5°); uv max (EtOH) 223 mμ (log ε 4.27), 234 (4.35), 257 (4.65), 331 (3.93), 441 (3.91); ir (KBr) 1600 cm^{-1} (C=O); nmr ($CDCl_3$) δ 10.1 (t, 1, NH), 8.40 (m, 1, peri H), 7.30 (m, 4, aromatic H), 6.30 (d, 1, aromatic H), 4.60 (s, 2, CH_2O), 3.76 (s, 1, OH), 2.33–3.50 (m, 8, 4 NCH_2), 1.08 (t, 6, 2 CH_3).

Anal. Calcd for $C_{20}H_{24}N_2O_2S$: C, 67.38; H, 6.78; N, 7.85; S, 8.99. Found: C, 67.20; H, 6.76; N, 7.85; S, 9.05.

Registry No.—**1**, 38605-72-0; **2**, 6469-87-0; **3**, 13420-58-1; **5**, 38615-62-2; **7**, 3105-97-3; **8**, 38615-64-4; **8** 2HCl, 38615-65-5; **9**, 38615-66-6; **9** HCl, 38615-67-7; **10**, 3613-13-6; **11**, 32484-50-7; thiophenol, 108-98-5; 2,6-dichlorobenzonitrile, 1194-65-6; thiosalicylic acid, 147-93-3; *m*-bromochlorobenzene, 106-37-2; *N,N*-diethyl-*N'*-methylethylenediamine, 104-79-0.

Acknowledgments.—The authors wish to express appreciation to our associates, Drs. R. Kullnig and S. Clemans and their coworkers, for the spectroscopic data reported in this paper.

Synthesis of Aminobenzofurans and Aminonaphtho[1,2-*b*]furans

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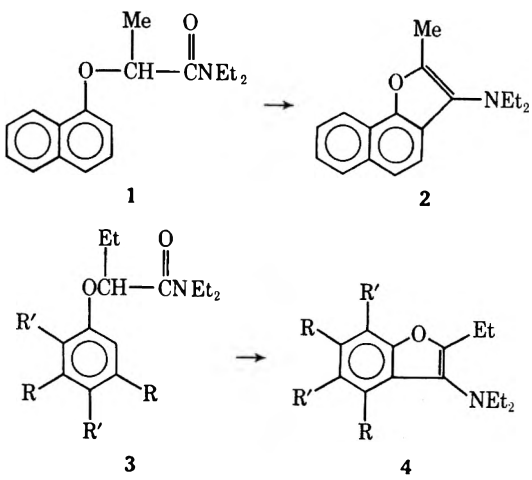
The synthesis of benzofurans and naphthofurans by the ring closure of α-aryloxy carbonyl compounds and their corresponding acetals has been well documented.[1] However, the ring closure of α-aryloxyamides has not been presented. We wish to report a new synthesis of aminonaphtho[1,2-*b*]furan (2) and aminobenzofurans (4) by a cyclodehydration of aryloxyamides.[2,3] When *N,N*-diethyl-2-(1-naphthyloxy)propionamide (1) was treated with phosphorus oxychloride, compound 2 was isolated in 90% yield. The mass spectrum of 2 gave a molecular ion at *m/e* 253 which is equivalent to a loss of water from 1. The ir spectrum of 2 showed no carbonyl group. The nmr spectrum of 2 showed a sharp singlet at δ 2.50 ppm corresponding to a methyl group, and the aromatic protons were reduced from seven to six protons. From a comparison of the aromatic region of the nmr spectra of 1 (δ 6.72–8.40 ppm) and 2 (δ 7.22–8.35 ppm), it is obvious that the proton at the 2 position was replaced.[4] These spectral data suggest 2 to be 2-methyl-3-(*N,N*-diethylamino)naphtho[1,2-*b*]furan. Similarly, the reaction of aryloxyamides 3 gave benzofurans 4.



a, R = Cl; R' = H
b, R = H; R' = Cl

The reaction is believed to involve an electrophilic attack by the carbonyl carbon at a position ortho to the ether group. Attempts were made to use phosphorus pentoxide, zinc chloride, and polyphosphoric acid as dehydrating agents, but the yield was poor.

Experimental Section

The nmr spectra were obtained on a Varian HA-60-IL spectrometer in deuteriochloroform solution with tetramethylsilane as an internal reference. The mass spectra were measured on a Varian MAT CH-5 spectrometer. Melting points are uncorrected. Elemental analyses were performed on a Perkin-Elmer 240 Elemental Analyzer.

Preparation of α-Aryloxyamides. General Procedure.—The α-aryloxy acids were prepared from the corresponding phenol or naphthol and the α-halo acid according to the procedure of Koelsch.[5] The α-aryloxy acids were converted to their corresponding acid chlorides by reaction with phosgene at 50° in toluene using 0.1 mol of dimethylformamide per 1 mol of acid. After HCl evolution ceased, excess phosgene was removed by purging with dry nitrogen. The α-aryloxyamides were prepared by addition of the acid chloride solution to a mixture of diethylamine and triethylamine (each in 10% excess) in toluene at 10–15°. After complete acid chloride addition, the solution was stirred at 45° for 1 hr. Upon cooling, the reaction mixture was washed successively with 2% HCl solution and water. The organic phase was dried over anhydrous magnesium sulfate and then evaporated to obtain α-aryloxyamides. Compounds 1, 3a, and 3b prepared in this method are listed in Table I.

TABLE I
PREPARATION OF α-ARYLOXYAMIDES[a]

Compd	Yield, %	Mp or bp, °C (mm)
1	98	78–79
3a	82	63.5–64.5
3b	84	133–135 (0.06)

[a] Satisfactory analytical values (±0.35% for C, H) were reported for 1, 3a, and 3b.

Preparation of Aminobenzofurans and Aminonaphtho[1,2-*b*]furans. General Procedure.—The aryloxyamide (0.05 mol) and phosphorus oxychloride (0.15 mol) in 50 ml of toluene were refluxed for 5 hr. The resulting reaction mixture was quenched in cold water (15–20°) and then treated with 100 ml of 5% sodium carbonate solution. The toluene layer was separated, dried over anhydrous magnesium sulfate, and then evaporated to obtain an oil which was either distilled under reduced pressure or purified by tlc.

2-Methyl-3-(*N,N*-diethylamino)naphtho[1,2-*b*]furan (2) had nmr spectrum ($CDCl_3$) δ 1.00 (t, 6 H, methyl), 2.50 (s, 3 H, methyl), 3.15 (q, 4 H, methylene), and 7.22–8.35 (m, 6 H, aromatic); mass spectrum *m/e* 253 (parent ion); picrate (ethanol) mp 154–155°.

Anal. Calcd for $C_{23}H_{22}N_4O_8$: C, 57.26; H, 4.56; N, 11.62. Found: C, 57.34; H, 4.52; N, 11.60.

(1) R. C. Elderfield and V. B. Meyer, "Heterocyclic Compounds," Vol. 2, R. C. Elderfield, Ed., Wiley, New York, N. Y., 1951, p 15.
(2) C. K. Tseng, J. H. Chan, D. R. Baker, and F. H. Walker, *Tetrahedron, Lett.*, 3053 (1971).
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(4) J. W. Emsley, S. R. Salman, and R. A. Storey, *J. Chem. Soc. B*, 1513 (1970).
(5) C. F. Koelsch, *J. Amer. Chem. Soc.*, **53**, 304 (1931).

2-Ethyl-3-(*N*,*N*-diethylamino)-4,6-dichlorobenzofuran (4a) had nmr spectrum ($CDCl_3$) δ 0.95 (t, 6 H, methyl), 1.25 (t, 3 H, methyl), 2.79 (q, 2 H, methylene), 3.08 (q, 4 H, methylene), 7.18 (d, 1 H, aromatic), and 7.28 (d, 1 H, aromatic); picrate (ethanol) mp 148.5–149.5°.

Anal. Calcd for $C_{20}H_{20}N_4O_8Cl_2$: C, 46.60; H, 3.88; N, 10.87. Found: C, 46.30; H, 3.81; N, 10.72.

2-Ethyl-3-(*N*,*N*-diethylamino)-5,7-dichlorobenzofuran (4b) had nmr spectrum ($CDCl_3$) δ 0.91 (t, 6 H, methyl), 1.24 (t, 3 H, methyl), 2.77 (q, 2 H, methylene), 3.03 (q, 4 H, methylene), 7.17 (d, 1 H, aromatic), and 7.40 (d, 1 H, aromatic); picrate (ethanol) mp 172–173°.

Anal. Calcd for $C_{20}H_{20}N_4O_8Cl_2$: C, 46.60; H, 3.88; N, 10.87. Found: C, 46.15; H, 3.87; N, 10.68.

Registry No.—**1**, 15299-99-7; **2**, 38740-02-2; **2** picrate, 38740-03-3; **3a**, 38740-04-4; **3b**, 38740-05-5; **4a**, 38740-06-6; **4a** picrate, 38740-07-7; **4b**, 38740-08-8; **4b** picrate, 38740-09-9.

Reexamination of the Claisen–Schmidt Condensation of Phenylacetone with Aromatic Aldehydes[1]

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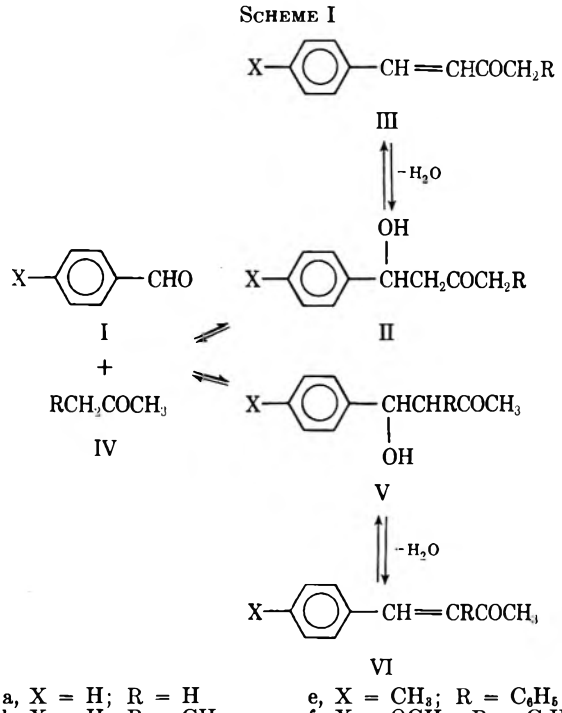
Although the base-catalyzed reaction of aldehydes with ketones of the type RCH_2COCH_3 can, in principle, occur with two possible orientations (Scheme I) the

SCHEME I



a, X = H; R = H
b, X = H; R = CH_3
c, X = OCH_3; R = H
d, X = H; R = C_6H_5
e, X = CH_3; R = C_6H_5
f, X = OCH_3; R = C_6H_5
g, X = Cl; R = C_6H_5
h, X = NO_2; R = C_6H_5

condensation of aromatic aldehydes with such ketones usually occurs at the methyl group.[2] It has been shown[3-6] that the rate-determining step in reactions of this type involves the condensation process, namely, attack by an enolate ion of IV at the carbonyl group of I. In basic solution methyl-*n*-alkyl ketones form approximately equal amounts of the two isomeric enolates while branched alkyl groups favor the less highly substituted enolate;[7] hence a mixture of both unsaturated ketones, III and VI, would be expected from the base-catalyzed condensations of the ketones IV with aldehydes. Because this is not the case, the *product*-determining step is believed to involve large rate differences in the competing dehydrations of the intermediate ketols, II and V. For example, the reaction of 2-butanone (IVb) with benzaldehyde affords the unsaturated ketone IIIb exclusively.[4,5] Independent synthesis of ketols IIb and Vb followed by treatment with base revealed that Vb retrogressed to reactants[5] while both dehydration and retrogression occurred with IIb.[4,5] The exclusive formation of methyl condensation products is usually observed only when reaction conditions are vigorous enough to cause dehydration of the intermediate ketols. Under milder conditions ketols II and V can both be isolated in reactions of aromatic aldehydes with 2-butanone.[5,8,9] The preferential cleavage of type V ketols to reactants has been attributed to steric hindrance to dehydration imposed by bulky R groups.[4,5,10,11]

A reaction frequently cited[12,13] as involving exclusive methyl condensation is the hydroxide-catalyzed condensation of phenylacetone (IIId) with benzaldehyde;[14,15] substituted benzaldehydes have also been reported to afford unsaturated ketones corresponding to methyl condensation only.[16] Since the more highly substituted enolate of phenylacetone is strongly favored in basic solution[7] these results have prompted the belief[12,13] that ketol Vd must undergo retrogression in preference to dehydration.

We have examined the base-catalyzed reaction of phenylacetone with several aromatic aldehydes under similar conditions to those reported previously and have quantitatively determined the components of the crude products using glc and nmr analysis. In every reaction but one, unsaturated ketones corresponding to both possible modes of condensation were produced. The results are shown in Table I.[17] The relative mole ratios of III:VI were determined by glc analysis, using pure samples of the unsaturated ketones as standards. Samples of VI were prepared independently by the piperidine-catalyzed condensa-

(1) The receipt of a Lafayette College Research Fund grant in support of this research is gratefully acknowledged.

(2) A. T. Nielsen and S. J. Houlihan, "Organic Reactions," Vol. 16, Wiley, New York, N. Y., 1968, and references cited therein.

(3) J. D. Gettler and L. P. Hammett, *J. Amer. Chem. Soc.*, **65**, 1824 (1943).

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(7) H. O. House and V. Kramar, *J. Org. Chem.*, **28**, 3362 (1963).

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(9) H. Midorikawa, *Bull. Chem. Soc. Jap.*, **27**, 131 (1954).

(10) M. R. F. Ashworth and J. E. Dubois, *Bull. Soc. Chim. Fr.*, 147 (1955).

(11) C. S. Rondestvedt and M. E. Rowley, *J. Amer. Chem. Soc.*, **78**, 3804 (1956).

(12) Reference 2, p 35.

(13) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 222.

(14) P. L. Southwick, L. A. Pursglove, and P. Numerof, *J. Amer. Chem. Soc.*, **72**, 1604 (1950).

(15) G. Goldschmiedt and H. Krczmar, *Monatsh. Chem.*, **22**, 659 (1901).

(16) G. Goldschmiedt and H. Krczmar, *Monatsh. Chem.*, 749 (1901).

(17) See Experimental Section.

TABLE I

BASE-CATALYZED REACTION OF PHENYLACETONE WITH SUBSTITUTED BENZALDEHYDES, p-XC_6H_4CHO

Registry no.	X	Reaction temp, °C	Reaction time, hr	Relative mole ratio III:VI	Total yield[a] of III + VI, %	Yield of isolated III, %
100-52-7	H	65	18	91:9	92	44
104-87-0	CH_3	65	18	92:8		19
	CH_3	80	24	90:10	88	50
123-11-5	OCH_3	65	18	90:10		24
	OCH_3	80	24	90:10	88	43
104-88-1	Cl	65	18	87:13	68	24
555-16-8	NO_2	Various[b]	Various[b]	Trace VIh		0

[a] Determined by glc and nmr analysis, as detailed in Experimental Section. [b] Reference 17.

tion of phenylacetone with the appropriate aromatic aldehyde, a procedure which has previously been found to produce condensation at the methylene group[18-20] and subsequent formation of the cis-diaryl alkene when R is phenyl.[18,21] Work-up of the hydroxide-catalyzed reaction mixtures afforded pure samples of III, invariably the major product of these reactions. The structures of all products were verified *via* nmr and ir, as well as elemental analysis for new compounds.

The results show no significant variation in the relative yields of the isomeric ketones with changes in aldehyde structure, the relative mole ratio of III to VI being approximately 9:1 for four of the five aldehydes. Increasing the temperature in two of the reactions also caused no significant change in relative product yields. In other reactions of aldehydes with methyl alkyl ketones higher temperatures have been found to favor methyl condensation.[22] Apparently, base-catalyzed dehydration of V relative to II is more favorable when R is phenyl than when R is methyl, a conclusion which suggests that electronic effects play a role in the dehydration step along with steric effects. In particular the transition states in the dehydration of ketols Vd-h are stabilized more when R = phenyl than when R = CH_3; no such difference in transition state stabilities is expected in the dehydration of ketols IId-h.[23] As a result, the ratio of rate constants $k_{V\rightarrow VI}/k_{II\rightarrow III}$ should increase with a change in R from methyl to phenyl. Competing with this favorable electronic effect is unfavorable steric interference from the phenyl group in Vd-h, a factor absent in ketols IId-h.[24]

The independence of relative yields of III:VI to the para substituent, X, is probably an indication that any electronic effects caused by variations in X are exerted to the same extent on the dehydration and retrogression steps of both ketols II and V. It is relevant that ketols Va and Vc exhibited nearly identical ratios of dealdolization to dehydration on treatment with dilute NaOH.[4] The rates of both reactions were larger for the p-methoxy compound, which was attributed to the fact that both dealdolization and dehydration lead to more effectively resonance-stabilized products when X is p-methoxy than when X is hydrogen.

(18) H. E. Zimmerman, L. Singer, and B. S. Thyagarajan, *J. Amer. Chem. Soc.*, **81**, 108 (1959).

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(20) I. M. Heilbron and F. Irving, *J. Chem. Soc.*, 931, 936 (1929).

(21) R. A. Abramovitch and A. Obach, *Can. J. Chem.*, **37**, 502 (1959).

(22) Reference 2, p 77.

(23) This conclusion would be valid for either an E2 or an E1cb transition state.

(24) It is also likely, although the consequences are uncertain, that the location of the phenyl group in V would stabilize the enolate in which dehydration occurs, namely p-$XC_6H_5CH(OH)C(C_6H_5)=COCH_3^-$. In contrast, the favored enolate of II, p-$XC_6H_5CH(OH)CH_2CO=CHC_6H_5^-$ is not the one in which dehydration can occur.

Experimental Section[25]

A. Synthesis of 1-(p-X-Phenyl)-2-phenyl-1-buten-3-ones. 1,-2-Diphenyl-1-buten-3-one (VId) was prepared by the method of Zimmerman, *et al.*:[18] bp 127–132° (0.6 mm); mp 54–55° (lit.[18] mp 55–56°); nmr δ 7.56 (s, 1, -CH=), 7.1 (m, 10, aryl H), 2.22 (s, 3, CH_3).

1-p-Tolyl-2-phenyl-1-buten-3-one (VIe).—A mixture of phenylacetone (15.6 g, 0.116 mol), p-tolualdehyde (13.9 g, 0.116 mol), and piperidine (0.24 g) in 80 ml of dry benzene was refluxed for 19 hr using a Dean–Stark trap. Evaporation of solvent under reduced pressure followed by vacuum distillation gave 16.9 g (62%) of light yellow oil, bp 140–145° (0.5 mm), which solidified on standing. Recrystallization from petroleum ether (bp 60–110°) afforded white needles: mp 64–65°; ir 1655 cm^{-1} (C=O); nmr δ 7.62 (s, 1, -CH=), 7.2 (m, 9, aryl H), 2.26 (s, 3, CH_3), 2.20 (s, 3, CH_3).

Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.82. Found: C, 86.55; H, 6.94.

1-p-Methoxyphenyl-2-phenyl-1-buten-3-one (VIf) was prepared by the same method as VIe from p-anisaldehyde (15.6 g, 0.116 mol) with a 24-hr reflux period. Vacuum distillation of crude product gave 15.5 g (53%) of viscous yellow oil, bp 159–164° (0.6 mm) [lit.[26] bp 218–220° (8–10 mm)], which gradually crystallized on refrigeration. Recrystallization from petroleum ether (bp 38–50°) afforded white needles: mp 61–63° (lit.[24] mp 63–64°); ir 1658 cm^{-1} (C=O); nmr δ 7.60 (s, 1, -CH=), 7.0 (m, 9, aryl H), 3.66 (s, 3, OCH_3), 2.24 (s, 3, $COCH_3$).

1-p-Chlorophenyl-2-phenyl-1-buten-3-one (VIg) was prepared by the same method as VIe from p-chlorobenzaldehyde (16.3 g, 0.116 mol). The crude product, a solid, was recrystallized from ethanol, affording light tan needles (16.8 g, 56%): mp 125–126.5°; ir 1660 cm^{-1} (C=O); nmr δ 7.56 (s, 1, -CH=), 7.2 (m, 9, aryl H), 2.27 (s, 3, CH_3).

Anal. Calcd for $C_{16}H_{13}ClO$: C, 74.86; H, 5.10; Cl, 13.81. Found: C, 74.86; H, 5.25; Cl, 13.65.

1-p-Nitrophenyl-2-phenyl-1-buten-3-one (VIh) was prepared from p-nitrobenzaldehyde (8.76 g, 0.058 mol), phenylacetone (7.78 g, 0.058 mol), piperidine (0.14 ml), and hexanoic acid (0.07 ml) in dry benzene (40 ml). After 18 hr more piperidine (0.18 ml) was added and the solution was refluxed for 20 hr longer. The crude product was vacuum distilled and the fraction with bp 184–195° (0.7 mm) was collected as an orange oil (3.7 g, 24%) which rapidly solidified. Recrystallization from ethanol and then from petroleum ether (bp 60–110°) gave yellow leaflets: mp 110–112°; ir 1668 cm^{-1} (C=O); nmr δ 8.0 and 7.3 (m, ~9, aryl H), 7.61 (s, 1, -CH=), 2.31 (s, 3, CH_3).

Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 72.11; H, 5.06; N, 4.97.

(25) Melting points were taken on a Fisher-Johns block and are uncorrected. Infrared spectra were determined in $CHCl_3$ on a Beckman IR-10 instrument and were calibrated against the 1601-cm^{-1} peak of polystyrene. Nmr spectra were recorded in $CDCl_3$ on either a Perkin-Elmer R-24 instrument or on a JEOL MH-60 spectrometer. Glc analyses were performed on a Carle Model 8000 gas chromatograph using a 6 ft × 0.125 in. 8% G.E. SF96 on 90–100 mesh Anakrom ABS column. Elemental microanalyses were performed by Dr. G. I. Robertson, Jr., Florham Park, N. J.

(26) T. N. Ghosh, A. Bose, and A. Raychaudhuri, *J. Indian Chem. Soc.*, **37**, 93 (1960).

B. Base-Catalyzed Reactions of Phenylacetone with Para-Substituted Benzaldehydes. Reaction of Phenylacetone with Benzaldehyde.—Phenylacetone (24.9 g, 0.186 mol) and benzaldehyde (19.7 g, 0.186 mol) were added to a rapidly mechanically stirred solution of NaOH (1.50 g) in water (800 ml) at 65°. After 18 hr the mixture was cooled to room temperature and extracted with five 100-ml portions of CH_2Cl_2. The extract was washed with water and dried ($MgSO_4$) and solvent was evaporated under reduced pressure. A small sample of the crude product was set aside for glc and nmr analysis. The remainder of the product was recrystallized from methanol, affording 18.2 g (44%) of *trans*-1,4-diphenyl-3-buten-2-one (IIId): mp 72–75° (lit.[27] mp 73–76°); nmr δ 7.57 (d, 1, J = 16 Hz) and 6.70 (d, 1, J = 16 Hz) (trans CH=CH), 7.3 (m, 10, aryl H), 3.82 (s, 2, CH_2).

Glc analysis of the *crude* product showed a relative yield of 91:9 of IIId:VId; glc and nmr analysis[28] showed a total yield of 92% for IIId + VId.[29]

Reaction of Phenylacetone with *p*-Tolualdehyde.—The same procedure as with benzaldehyde was followed. Washing of the crude product with petroleum ether (bp 20–40°) and recrystallization from ethanol afforded 8.2 g (19%) of *trans*-1-phenyl-4-(*p*-tolyl)-3-buten-2-one (IIIe): mp 112.5–114° (lit.[16] mp 115°); nmr δ 7.57 (d, 1, J = 16 Hz) and 6.66 (d, 1, J = 16 Hz) (trans CH=CH), 7.2 (m, ~9, aryl H), 3.84 (s, 2, CH_2), 2.26 (s, 3, CH_3). Repetition of the reaction at 80° for 24 hr increased the yield to 21.9 g (50%).

Glc and nmr analysis of the crude products, as above, showed a relative yield of 92:8 for IIIe:VIe for the 65° reaction and 90:10 for the 80° reaction. A total yield (IIIe + VIe) of 88% was found in the latter reaction.

Reaction of Phenylacetone with *p*-Anisaldehyde.—The standard procedure was followed. Trituration of the crude product with cold ether and filtration afforded 11.2 g (24%) of *trans*-4-(*p*-anisyl)-1-phenyl-3-buten-2-one (IIIf): mp 98–100° (lit.[16] mp 98–100°); nmr δ 7.58 (d, 1, J = 16 Hz) and 6.62 (d, 1, J = 16 Hz) (trans CH=CH), 7.25 (m, ~9, aryl H), 3.87 (s, 2, CH_2), 3.72 (s, 3, OCH_3).

Glc and nmr analysis of the crude products showed relative yields of 90:10 for IIIf:VIf in both reactions. The total yield (IIIf + VIf) was 88% in the 80° reaction.

Reaction of Phenylacetone with *p*-Chlorobenzaldehyde.—The standard procedure was used. Two recrystallizations of the crude product from ethanol gave 11.4 g (24%) of *trans*-4-(*p*-chlorophenyl)-1-phenyl-3-buten-2-one (IIIg) as white crystals: mp 102–104°; ir 1655 cm^{-1} (C=O), 970 (trans CH=CH); nmr δ 7.53 (d, 1, J = 16 Hz) and 6.66 (d, 1, J = 16 Hz) (trans CH=CH), 7.27 (m, 9, aryl H), 3.89 (s, 2, CH_2).

Anal. Calcd for $C_{16}H_{13}ClO$: C, 74.85; H, 5.10; Cl, 13.81. Found: C, 74.77; H, 5.02; Cl, 13.80.

Glc and nmr analysis of the crude product showed a ratio of IIIg:VIg of 87:13. A total yield (IIIg + VIg) of 68% was found.

Reaction of phenylacetone with *p*-nitrobenzaldehyde at temperatures varying from 50 to 75° and times of 6–24 hr afforded either unreacted starting materials and/or a dark red glassy substance which could not be purified. Glc analysis of the crude products showed a trace of VIh but no products other than starting materials could be detected.[30]

(27) S. A. Fine and R. L. Stern, *J. Org. Chem.*, **32**, 4132 (1967).

(28) Glc analyses were based on comparisons of peak areas of standardized solutions of the pure compounds with peak areas in solutions of the crude product mixtures. Nmr analysis was used as confirmatory evidence. The areas of suitable peaks due to III and VI in the nmr spectrum of the crude product mixtures were compared with the areas of peaks due to unreacted phenylacetone and/or unreacted aldehyde. Total yields obtained by the two methods always differed by less than 4%.

(29) Since the glc retention times of VId–h in the crude product mixtures were precisely the same as the retention times of authentic samples, and since the nmr shifts due to VId–h in the crude product mixtures were identical with those in authentic samples, we conclude that the stereochemistry of VI in our product mixtures is identical with that of the authentic samples, namely cis with respect to the aryl groups. Similar stereochemical results have been observed in a related base-catalyzed condensation: H. E. Zimmerman and L. Ahramjian, *J. Amer. Chem. Soc.*, **81**, 2086 (1959).

(30) The retention times of type VI ketones (d–g) were almost exactly double the retention times of the corresponding type III ketones under the conditions used. The conclusion that IIIh was absent is based on the fact that no peak appeared on the chromatogram even after 15 times the retention time of VIh.

Registry No.—IIId, 38661-84-6; IIIe, 38661-85-7; IIIf, 38661-86-8; IIIg, 37562-70-2; IVd, 103-79-7; VId, 38661-88-0; VIe, 38661-89-1; VIf, 13938-22-2; VIg, 38661-91-5; VII, 8661-92-6.

A Reinvestigation of the Condensation of Aliphatic Ketones with Benzil

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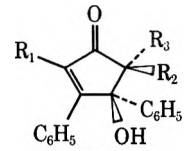
An extensive investigation of the base-catalyzed condensation of acetone and other aliphatic ketones with benzil was carried out many years ago by Japp and his coworkers.[1] The product from the reaction of acetone with benzil was proved to be 4-hydroxy-3,4-diphenyl-2-cyclopenten-1-one (**1**). From the reaction of other aliphatic ketones with benzil, cyclopentenones bearing alkyl groups at C-2 or C-5 were obtained. The structures of these products, however, were not completely established. In the present study some of these products were reinvestigated, and their structures were determined using nmr spectroscopy.

The structure of **1** and that of **2**, which is produced from 3-methyl-2-butanone, are unambiguous, and these compounds serve as models. In addition to signals for aromatic and hydroxylic hydrogens, the spectrum of **1** has a one-proton singlet at δ 6.66 and an AB pattern [δ_A 2.98, δ_B 2.84 (J_{AB} = 19 Hz)]. The spectrum of **2** has a one-proton singlet at δ 6.74 and three-proton singlets at 1.32 and 0.64. The substituents at C-4 cause these latter to be displaced from δ 1.03, the reported position for the methyl hydrogen resonance of 5,5-dimethyl-2-cyclopenten-1-one.[2] The methyl group cis to the phenyl group on C-4 lies in the region shielded by the aromatic ring, and this methyl group thus gives rise to the higher field peak.[3]



1, $R_1 = R_2 = R_3 = H$
2, $R_1 = H$; $R_2 = R_3 = CH_3$
3, $R_1 = R_2 = CH_3$; $R_3 = H$
4, $R_1 = R_3 = CH_3$; $R_2 = H$
5, $R_1 = CH_3$; $R_2 = R_3 = H$
6, $R_1 = R_3 = H$; $R_2 = CH_3$
7, $R_1 = R_2 = H$; $R_3 = CH_3$

From the reaction of 3-pentanone with benzil Japp and Meldrum obtained two products, one melting at 150° and the other at 128.°[1a] They concluded

(1) (a) F. R. Japp and A. N. Meldrum, *J. Chem. Soc.*, **79**, 1024 (1901); (b) F. R. Japp and J. Knox, *ibid.*, **87**, 673 (1905); (c) F. R. Japp and A.C. Michie, *ibid.*, **83**, 276 (1903).

(2) T. Matsumato, H. Shirahama, A. Ichihara, H. Shin, S. Kagawa, N. Ito, T. Hisamitau, T. Kamada, and F. Sakan, *Tetrahedron Lett.*, 4097 (1967).

(3) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, p 234.

that the product of higher melting point is a cyclopentenone bearing methyl groups at C-2 and C-5 and that the other product is an acyclic compound, 3-methyl-1,2-diphenyl-2-hexene-1,4-dione. The nmr spectra of these compounds clearly show that the two are, in fact, diastereoisomeric. Each has a three-proton singlet near δ 2.0 and a one-proton quartet and a three-proton doublet. The spectrum of the higher melting product has the doublet at δ 1.24, and the compound is therefore **3** with the methyl group on C-5 trans to the phenyl group on C-4. The spectrum of the other isomer has the doublet at δ 0.74, and the compound is therefore **4**.

The compounds equilibrate under basic conditions, and the equilibrium mixture in ethanol contains very nearly equal amounts of the two. That the two are of nearly equal stability is surprising since one would expect steric interference of the methyl group with phenyl to be far more severe than interference of methyl with hydroxyl. A reasonable explanation is that clustering of solvent molecules about the hydroxyl group increases its apparent size. Although the equilibrium mixture contains nearly equal amounts of the two compounds, in preparative experiments **3** is produced in nearly quatitative yield because this more insoluble compound preferentially crystallizes from the basic solution.

Condensation of 2-butanone with benzil can give three different monomethyl-substituted products. When the reaction was carried out in dilute alcoholic potassium hydroxide, Japp and Meldrum obtained a product melting at 118° to which they assigned structure **5**.[1a,4] The nmr spectrum clearly confirms the correctness of the assignment of structure. The spectrum has an easily exchangable one-proton singlet, a two-proton singlet at δ 2.96 (accidentally equivalent methylene protons), and a three-proton singlet at 1.93.[5a] From a heterogeneous reaction carried out in the presence of hot concentrated aqueous base, Japp and Meldrum obtained, in addition to **5**, a compound melting at 180° and a small amount of a compound melting at 157°.[1a] They concluded that the higher melting product is a cyclopentenone with a methyl group at C-5 and that the compound melting at 157° is 1,2-diphenyl-2-hexene-1,4-dione. The nmr spectra of the compounds show them to be diastereoisomeric. In addition to signals for aromatic and hydroxylic hydrogens, each has a one-proton singlet near δ 6.8 and a one-proton quartet and a three-proton doublet. The doublet in the spectrum of the higher melting compound lies at δ 1.24, and the compound is **6**. The doublet at δ 0.72 in the spectrum of the other compound proves it to be **7**, the diastereomer of **6**.

In agreement with the properties of the related dimethyl compounds, an equilibrium mixture of **6** and **7** in ethanolic base contains appreciable amounts of both isomers, but the higher melting **6** preferentially crystallizes. Compounds **6** and **7** are not readily interconverted with the structurally isomeric **5**. Compound **5** was unaffected by base, and appreciable conversion of a mixture of **6** and **7** to **5** was accomplished only by heating in 1 *M* ethanolic potassium hydroxide for an extended period during which extensive destruction of the compounds took place. Since these conditions are far more vigorous than those under which the three compounds are formed in the same reaction mixture, the production of the structurally isomeric compounds is the result of independent, rather than consecutive reactions.

The uv absorption maximum of those compounds which have hydrogen at C-2 occurs near 285 nm. The maximum lies near 275 nm for the compounds in which C-2 bears a methyl group. The explanation, given some years ago, for these observations is that the alkyl group interferes with the ability of the phenyl group on C-3 and the cyclopentenone ring to be coplanar.[6]

Experimental Section

All melting points are uncorrected. The nmr spectra were recorded on a Perkin-Elmer Model R12A instrument, and chemical shifts are reported in parts per million downfield from internal tetramethylsilane. The ir spectra were taken on a Perkin-Elmer Model 467 grating instrument, and uv spectra were recorded on a Cary 14 spectrophotometer.

The following compounds were prepared by published procedures. **4-Hydroxy-3,4-diphenyl-2-cyclopenten-1-one** (**1**): mp 147–148° (lit.[1b] mp 149°); nmr ($CDCl_3$) δ 7.2–7.7 (m, 10), 6.66 (s, 1), 3.53 (s, 1, OH), 2.91 (AB q, 2, Δ_{AB} = 8 Hz, J_{AB} = 19 Hz); uv max (95% EtOH) 288 nm (log ϵ 4.26); ir ($CHCl_3$) 3600, 3400, 1725 (sh), 1695 cm^{-1}. **4-Hydroxy-5,5-dimethyl-3,4-diphenyl-2-cyclopenten-1-one** (**2**): mp 181–183° (lit.[1a] mp 181°); nmr ($CDCl_3$) δ 7.2–7.7 (m, 10), 6.74 (s, 1), 2.46 (s, 1, OH), 1.32 (s, 3), 0.64 (s, 3); uv max (95% EtOH) 287 nm (log ϵ 4.29); ir ($CHCl_3$) 3610, 3400, 1705 cm^{-1}. (4*SR*,5*SR*)-**4-Hydroxy-2,5-dimethyl-3,4-diphenyl-2-cyclopenten-1-one** (**3**): mp 150–151° (lit.[5] mp 152–153°); nmr ($CDCl_3$) δ 7.1–7.5 (m, 10), 2.71 (q, 1, J = 7 Hz), 2.32 (s, 1, OH), 1.98 (s, 3), 1.24 (d, 3, J = 7 Hz); uv max (95% EtOH) 275 nm (log ϵ 4.18); ir ($CHCl_3$) 3600, 3400, 1705 cm^{-1}. **4-Hydroxy-2-methyl-3,4-diphenyl-2-cyclopenten-1-one** (**5**): mp 116–118° (lit.[1a] mp 118°); nmr ($CDCl_3$) δ 7.0–7.5 (m, 10), 2.96 (s, 2), 2.57 (s, 1, OH), 1.93 (s, 3); uv max (95% EtOH) 276 nm (log ϵ 4.30); ir ($CHCl_3$) 3580, 3400, 1705 cm^{-1}. (4*SR*,5*SR*)-**4-Hydroxy-5-methyl-3,4-diphenyl-2-cyclopenten-1-one** (**6**): mp 182–183° (lit.[1a] mp 180°); nmr ($CDCl_3$) δ 7.2–7.7 (m, 10), 6.74 (s, 1), 2.68 (q, 1, J = 7 Hz), 2.35 (s, 1, OH), 1.24 (d, 3, J = 7 Hz); uv max (95% EtOH) 286 nm (log ϵ 4.32); ir ($CHCl_3$) 3600, 3400, 1705 cm^{-1}.

Preparation of (4*SR*,5*RS*)-4-Hydroxy-2,5-dimethyl-3,4-diphenyl-2-cyclopenten-1-one (**4**).—To a warm solution of 6.3 g of **3** in 25 ml of ethanol was added a solution of 2.5 g of KOH in 10 ml of ethanol. After 15 min the solution was slowly added to 5 ml of acetic acid in 25 ml of ethanol, and 100 ml of water was slowly added to the resulting solution. The precipitated product, 5.7 g, a 3:2 mixture of **4** and **3**, was filtered and dried. A portion of this product (0.69 g) was chromatographed on 50 g of silica gel. Elution by 1:150 ether–benzene gave **3** followed by a mixture of **3** and **4**. The latter was recrystallized twice from carbon tetrachloride–hexane to give 0.26 g of **4**: mp 129–130° (lit.[1a] mp 128°); nmr ($CDCl_3$) δ 7.0–7.5 (m, 10), 2.91 (q, 1, J = 7 Hz), 2.45 (s, 1, OH), 2.02 (s, 3), 0.74 (d, 3, J = 7 Hz); uv max (95% EtOH) 274 nm (log ϵ 4.12); ir ($CHCl_3$) 3580, 3400, 1705 cm^{-1}.

(4) Under the same conditions a few years later Japp and Michie obtained a product melting at 134° which they considered to be a second crystalline modification.[1b] In the present work only the product of lower melting point was obtained.

(5) (a) In a recent report it was mentioned briefly that reaction according to the original procedure gave 3-methyl-1,2-diphenyl-2-pentene-1,4-dione rather than **5**.[5b] No properties were given for the product, and the compound is not reported elsewhere in the literature. In the present work no difficulty was encountered in repeating the original experiment. A possible explanation for the discrepancy lies in the observation that under some conditions (*e.g.*, 21 mg/ml in CCl_4 at 35°) the signal for the hydroxylic proton is coincident with that for the accidentally equivalent methylene protons and the nmr spectrum of **5** contains two three-proton singlets. A deceptive spectrum and the tendency for **5** to remain noncrystalline may have caused misidentification of the product. (b) P. Bladon, S. McVey, P. L. Pauson, G. D. Broadhead, and W. M. Horspool, *J. Chem. Soc. C*, 306 (1966).

(6) P. Yates, N. Yoda, W. Brown, and B. Mann, *J. Amer. Chem. Soc.*, **80**, 202 (1958).

Preparation of (4*SR*,5*RS*)-4-Hydroxy-5-methyl-3,4-diphenyl-2-cyclopenten-1-one (7).—By a procedure analogous to that used to prepare **4**, **6** was isomerized to give a 6:5 mixture of **7** and **6**. Chromatography of 0.90 g of this mixture on 50 g of silica gel (elution with dilute ether in benzene mixtures) gave 0.24 g of **6**, followed by 0.36 g of a mixture of **6** and **7**, and finally 0.24 g of a 6:1 mixture of **7** and **6**. Four recrystallizations of the last from carbon tetrachloride gave 0.10 g of **7**: mp 159–160° (lit.[1a] mp 157°); nmr ($CDCl_3$) δ 7.2–7.7 (m, 10), 6.77 (s, 1), 2.92 (q, 1, J = 7 Hz), 2.88 (s, 1, OH), 0.72 (d, 3, J = 7 Hz); uv max (95% EtOH) 285 nm (log ε 4.29); ir ($CHCl_3$) 3600, 3400, 1705 cm^{-1}.

Equilibration of 3 and 4 in Basic Solution.—A solution of 0.23 g of **3** in 15 ml of ethanol was heated under reflux with 0.05 g of K_2CO_3. Aliquots were withdrawn at intervals and prepared for analysis by nmr by precipitation in water, extraction into ether, and evaporation of the ether. An equilibrium mixture containing 52% **4** and 48% **3** was formed after 90 min of heating. An identical mixture was formed by heating a 3:2 mixture of **4** and **3** in ethanol with K_2CO_3. A mixture containing a somewhat greater proportion of **4** was formed by allowing a solution of **3** in ethanol containing KOH to stand at room temperature. In another experiment, upon allowing a warm solution of 7.5 g of a mixture of **3** and **4** in 30 ml of ethanol containing 0.1 g of KOH to cool slowly, 5.5 g of a 16:1 crystalline mixture of **3** and **4** was slowly deposited. Analysis of the supernatant liquid at intervals showed it continuously to contain an equilibrium mixture of **3** and **4**.

Action of Base upon 5, 6, and 7.—A solution of 0.96 g of a mixture of **6** and **7** in 5 ml of 1 *M* ethanolic KOH was heated under reflux for 1 hr. The solution became very dark. After neutralization with acetic acid, the solution was poured into water, and the precipitated material was extracted into ether. The ether was evaporated, and 0.8 g of the residue was chromatographed on 45 g of neutral alumina (activity grade III). Eluted by benzene were 0.2 g of material, the ir spectrum of which lacked hydroxyl absorption, and 0.1 g of highly colored material. Eluted by 1:10 ether–benzene was 0.39 g of a mixture of **5**, **6**, and **7** which contained, according to analysis by nmr, 0.08 g of **5**. Other treatments of **5** and of mixtures of **6** and **7** did not effect interconversion of the structural isomers. Among the experiments in which no change was observed were treatment of **5** with boiling 1 *M* ethanolic KOH for 30 min, treatment of **5** with 0.1 *M* ethanolic KOH for 5 days, treatment of a mixture of **6** and **7** with 0.1 *M* ethanolic KOH for 5 days, and stirring, while heating under reflux, for 2 hr a heterogeneous mixture of 30% aqueous KOH and a solution of **6** and **7** in DME.

Registry No.—**1**, 5587-78-0; **2**, 38661-94-8; **3**, 38661-95-9; **4**, 38661-96-0; **5**, 38661-97-1; **6**, 38661-98-2; **7**, 38677-74-6; benzil, 134-81-6.

New Adducts of Hexafluoroacetone with Hydrogen Cyanide

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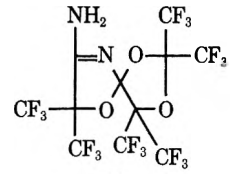
Received November 7, 1972

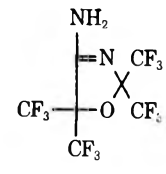
Two adducts of hexafluoroacetone with hydrogen cyanide are known. A 1:1 adduct, hexafluoroacetone cyanohydrin (**6**), was prepared by the piperidine-catalyzed addition of hydrogen cyanide to the ketone,[1] and a 2:1 adduct, 2,2,5,5-tetrakis(trifluoromethyl)-4-oxazolidinone (**4**), was prepared by reaction of hexafluoroacetone with sodium cyanide in acetonitrile.[2]

We noted that large, transparent crystals separated from a sample of hexafluoroacetone cyanohydrin that had been standing for more than a year in a clear glass bottle at room temperature. Elemental and mass spectral analysis showed that these crystals are a new, 3:2 adduct of hexafluoroacetone with hydrogen cyanide.

The spiro structure **1** was assigned to this 3:2 adduct on the basis of infrared and nmr spectral analysis. The ^{19}F nmr showed six nonequivalent CF_3 groups. The ^1H nmr showed two different absorptions of equal intensity that coalesced on warming, similar to the ^1H nmr spectrum of the closely analogous 4-amino-2,2,5,5-tetrakis(trifluoromethyl)-3-oxazoline (**2**).[3] The ir spectra of both **1** and **2** were also similar, with a band at 5.88 μ for C=N.



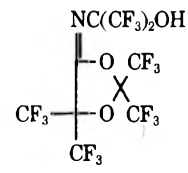
1



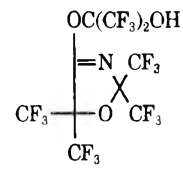
2

Chemically, the spiro compound **1** was also similar to **2**. Both compounds are stable to concentrated sulfuric acid at 100°, and both compounds are nitrated by fuming nitric acid in fuming sulfuric acid to form nitramines.

Attempts to prepare **1** under controlled conditions resulted in additional new adducts of hexafluoroacetone with hydrogen cyanide. A 3:1 adduct resulted when excess hexafluoroacetone was added to either hydrogen cyanide or the preformed cyanohydrin in the presence of basic catalyst at or below room temperature. The structure of this new adduct is believed to be the dioxolane **3** instead of the isomeric oxazoline **3a**, because attempts to distil the adduct



3



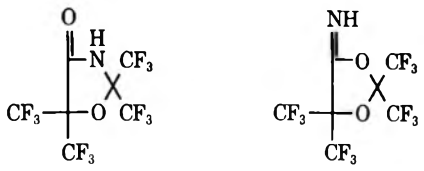
3a

at atmospheric pressure decomposed it to hexafluoroacetone and hexafluoroacetone cyanohydrin. Thermal decomposition of **3a** should result in hexafluoroacetone and 2,2,5,5-tetrakis(trifluoromethyl)-4-oxazolidinone, a compound known to possess high thermal stability.[2] Although this new 3:1 adduct is somewhat thermally unstable, it can be distilled at reduced pressure. It can be dissolved in cold alkali and reprecipitated with acid, but warm alkali converts it to the cyanohydrin. Methylation of **3** with diazomethane gives a stable *O*-methyl ether. Reaction of **3** with sodium hydride followed by acidification gives the 2:1 adduct **4**. Pyrolysis of **3** in the presence of a few drops of sulfuric acid gave a product that appeared to be a mixture of **3** and a new 2:1 adduct, **5**. Evidence

(1) I. L. Knunyants, E. M. Rokhlin, N. P. Gambaryan, Yu. A. Cheburkov and T-Y. Chen, *Khim. Nauka Prom.*, **4**, 802 (1959); *Chem. Abstr.*, **54**, 10851 (1959).

(2) W. J. Middleton and C. G. Krespan, *J. Org. Chem.*, **32**, 951 (1967).

(3) W. J. Middleton, D. Metzger, K. B. Cunningham, and C. G. Krespan, *J. Heterocycl. Chem.*, **7**, 1045 (1970).



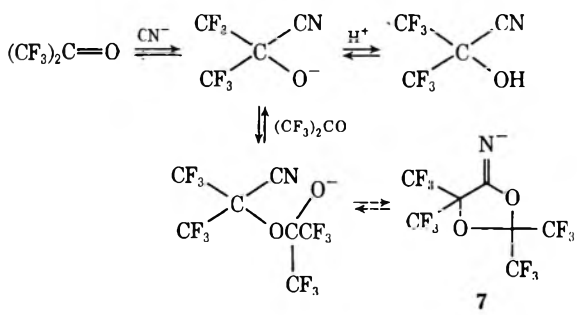
4 5

for formation of **5** consists of a new band in the ir spectrum at 5.73 μ, and two new absorptions in the ^{19}F nmr spectrum not due to the other known adducts.

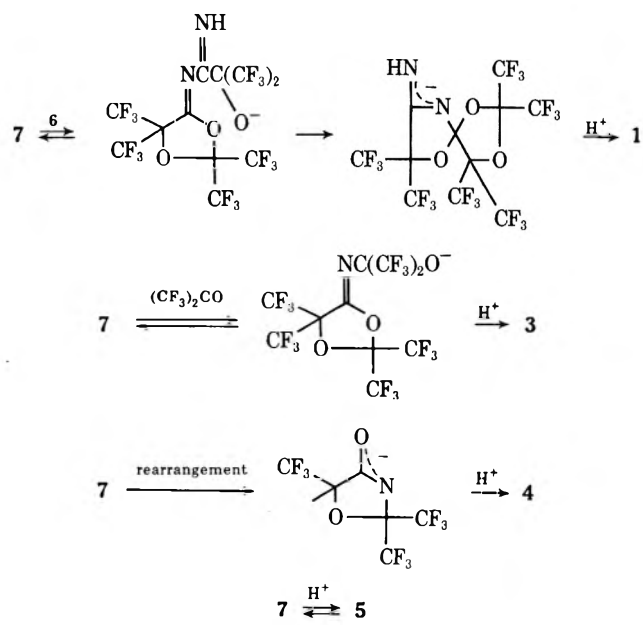
The 3:2 adduct **1** was eventually prepared in 40% yield by reaction of hexafluoroacetone cyanohydrin with excess hexafluoroacetone at 100° for 16 hr in the presence of an amine catalyst. Adduct **1** can also be prepared by adding trace amounts of amine to hexafluoroacetone cyanohydrin and allowing the equilibrating mixture to remain at room temperature for a prolonged period of time.

We believe that the very complex reactions of hexafluoroacetone with hydrogen cyanide to give the several different adducts (1:1, two 2:1, 3:1, and 3:2) can be represented by the following reaction schemes (Scheme I and II). Note that the intermediate anion

SCHEME I



SCHEME II



7 is common to all higher adducts. Which path the reaction takes depends on the temperature and the relative concentrations of catalyst, ketone, and hydrogen cyanide. All the adducts except the very unstable **5** can be prepared in pure form as the major product.

Experimental Section

8-Amino-2,2,4,4,7,7-hexakis(trifluoromethyl)-9-aza-1,3,6-trioxaspiro[4.4]non-8-ene (1).—A mixture of 19.3 g (0.10 mol) of hexafluoroacetone cyanohydrin,[1] 9.0 g (0.54 mol) of hexafluoroacetone, and 0.5 g of 1,4-diazabicyclo[2.2.2]octane (catalyst) was heated for 16 hr at 100° in a 125-ml Hastelloy-lined bomb. Excess hexafluoroacetone was allowed to evaporate and the residue was sublimed at 1 mm to give 10.9 g (40%) of **1** as a white, crystalline solid. Recrystallization from hexane gave the product as colorless prisms: mp 113–114°; ir (KBr) 5.86 μ; ^1H nmr (DMSO-d_6 at 30°) δ 8.60 (s) and 9.44 ppm (s); ^1H nmr (DMSO-d_6 at 50°) δ 9.12 ppm (broad s); ^{19}F nmr (acetone) δ −70.8 (A_3B_3, 6 F), −73.5 (A_3B_3, 6 F), and −78.3 ppm (A_3B_3, 6 F).

Anal. Calcd for $C_{11}H_2F_{18}N_2O_3$: C, 23.93; H, 0.36; F, 61.94; N, 5.07; mol wt, 552. Found: C, 23.71; H, 0.24; F, 61.93; N, 5.04; mol wt, 552 (mass spectrum).

Nitration of 1.—Red fuming nitric acid, 7 ml, was added to a solution of 2.76 g (0.005 mol) of **1** in 25 ml of fuming sulfuric acid (20% SO_3). The reaction mixture became warm. It was stirred for 5 min and then poured over ice. The white solid that formed was collected on a filter and recrystallized from benzene to give 1.70 g (58%) of 8-nitramino-2,2,4,4,7,7-hexakis(trifluoromethyl)-9-aza-1,3,6-trioxaspiro[4.4]non-8-ene (or tautomer) as colorless crystals: mp 43–44°; ir (KBr) 2.95 (NH) and 6.00 μ (C=N); uv (EtOH) λ_{max} 288 mμ (ϵ 12,200); ^{19}F nmr (CCl_3F) δ −71.3 (A_3B_3, 6 F), −74.0 (A_3B_3, 6 F), and −78.9 ppm (A_3B_3, 6 F).

Anal. Calcd for $C_{11}HF_{18}N_3O_5$: C, 22.12; H, 0.17; F, 57.27; N, 7.03; mol wt, 597. Found: C, 22.14; H, 0.43; F, 57.40; N, 6.87; mol wt, 597 (mass spectrum).

4-(1-Trifluoromethyl-1-hydroxy-2,2,2-trifluoroethylimino)-2,2,5,5-tetrakis(trifluoromethyl)-1,3-dioxolane (3). Method A.—Two drops of piperidine was added to a stirred mixture of 19.3 g (0.1 mol) of hexafluoroacetone cyanohydrin and 33.2 g (0.2 mol) of hexafluoroacetone cooled to −30°. The mixture solidified and the temperature rose to 15° in about 3 sec. There was obtained a quantitative crude yield of **3** as a colorless oil. A sample was purified by first dissolving it in cold 5% sodium hydroxide, and then precipitating it by adding 10% hydrochloric acid. The product was extracted with CCl_3F, and the extract was dried ($MgSO_4$) and then evaporated to dryness to give **3** as a colorless, crystalline solid, mp 29–30°.

Method B.—A mixture of 42 g (0.27 mol) of hexafluoroacetone, 4 ml (0.1 mol) of hydrogen cyanide, and a few crystals of potassium cyanide was sealed in a Carius tube at liquid nitrogen temperature. When the tube was warmed to room temperature and shaken, an exothermic reaction took place. Distillation gave 44 g (93%) of **3** as a colorless liquid, bp 58° (20 mm), $n^{25}D$ 1.3022. A 6-g sample was dissolved with cooling in 5 ml of 10% sodium hydroxide and 10 ml of water. Concentrated hydrochloric acid (2 ml) was added with cooling and the crystals that formed were collected on a filter and recrystallized from petroleum ether (bp 30–60°) to give 5.1 g of **3** as a colorless crystal: mp 29–30°; ir (neat) 5.61 μ (C=N); ^1H nmr (CCl_3F) δ 3.8 ppm (s); ^{19}F nmr (CCl_3F) δ −73.1 (septet, J = 5.5 Hz, 6 F), −78.8 (septet, J = 5.5 Hz, 6 F), and 80.0 ppm (s, 6 F).

Anal. Calcd for $C_{10}HF_{18}NO_3$: C, 22.88; H, 0.19; F, 65.14; N, 2.67. Found: C, 23.46; H, 0.54; F, 65.05; N, 2.80.

4-(1-Trifluoromethyl-1-methoxy-2,2,2-trifluoroethylimino)-2,2,5,5-tetrakis(trifluoromethyl)-1,3-dioxolane.—To 100 ml of dry ether and 19.3 g (0.1 mol) of hexafluoroacetone cyanohydrin at −30° was added 0.2 mol of hexafluoroacetone followed by 0.1 g of 1,4-diazabicyclo[2.2.2]octane. The mixture was brought to room temperature and filtered to remove a small amount of solid. A 3% solution of diazomethane in ether was added to the filtrate until no further evolution of nitrogen was observed, and the reaction mixture was distilled to give 17.5 g of the methyl ether as a colorless liquid: bp 135–148°; ir (neat) 5.63 μ (C=N); ^{19}F nmr (CCl_3F) δ −73.0 (septet, J = 6 Hz, 6 F), −75.7 (q, J = 1 Hz, 6 F), and −79.0 ppm (septet, J = 6 Hz, 6 F); ^1H nmr δ 3.63 ppm (septet, J = 1.0 Hz).

Anal. Calcd for $C_{11}H_3O_3NF_{18}$: C, 24.50; H, 0.56; F, 63.44; N, 2.60. Found: C, 24.38; H, 0.79; F, 63.30; N, 2.56.

Distillation of 3 from Acid.—A few drops of sulfuric acid was added to a crude sample of **3**, and the mixture was distilled to

give a liquid, bp 43° (10 mm). Analysis by glc, ir, and ^{19}F nmr indicated that two compounds were present in about equal amounts. One product was **3**. The other product (probably **5**) showed an ir band at 5.73 μ for C=N and two septets of equal intensity in the ^{19}F nmr spectrum. Attempts to isolate this second product were unsuccessful, for it apparently decomposes easily to hexafluoroacetone and hexafluoroacetone cyanohydrin.

Conversion of 3 to 2,2,5,5-Tetrakis(trifluoromethyl)-4-oxazolidinone (4) by Sodium Hydride.—A solution of 8.5 g of **3** in 10 ml of ethylene glycol dimethyl ether was added to a slurry of 1 g of sodium hydride in mineral oil (50%) in 15 ml of ethylene glycol dimethyl ether. The mixture was then warmed to 50° and the resulting solution was poured into ice and acidified with hydrochloric acid. The oil that formed was extracted with methylene chloride, dried, and distilled to give 3.2 g (38%) of **4**, bp 89° (20 mm), mp 104–106° (after recrystallization from benzene), identified by comparison with an authentic sample.[2]

Registry No.—**1**, 38868-31-4; **1** nitro derivative, 38868-32-5; **2**, 22038-16-0; **3**, 38868-34-7; **3** methyl ether derivative, 38868-35-8; **4**, 7730-28-1; **6**, 677-77-0; hexafluoroacetone, 684-16-2; hydrogen cyanide, 74-90-8.

Synthetic Reactions by Complex Catalsts. XXIX. Esterification of Carboxylic Acid with Alkyl Halide by Means of Copper(I)–Isonitrile Complex

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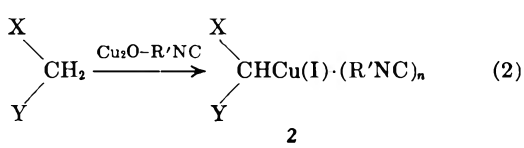
In a preliminary paper,[1] we have reported that carboxylic acid is readily esterified with alkyl halide in the presence of Cu_2O–isonitrile complex. A reaction scheme was presented in which Cu(I) carboxylate–isonitrile complex (**1**) was first generated from Cu_2O–isonitrile complex and carboxylic acid, and then **1** reacted with alkyl halide to produce the corresponding carboxylic ester (Scheme I).

SCHEME I

$$RCO_2H \xrightarrow{Cu_2O\text{–}R'NC} \underset{\mathbf{1}}{RCO_2Cu(I)\cdot(R'NC)_n} \xrightarrow{R''X} RCO_2R'' + Cu(I)X\cdot(R'NC)_n \quad (1)$$

In the present paper, we wish to report the isolation of Cu(I) carboxylate–isonitrile complex (**1**) as a key intermediate in the above reaction and the stereochemistry of the reaction. It is of interest to note that **1** in Scheme I constitutes a counterpart of organocopper(I)–isonitrile complex (**2**) derived from the reaction of acidic carbon acid such as acetylacetone and malonate with the Cu_2O–isonitrile complex.[2,3]



(2)

Isolation of Cu(I) Carboxylate–Isonitrile Complex.—On heating, Cu_2O was dissolved in acetic acid in the presence of *tert*-butyl isocyanide under nitrogen. From the reaction mixture, Cu(I) acetate–*t*-BuNC complex (**3**) was isolated. **3** is a white, crystalline

$$\underset{\mathbf{3}}{CH_3COOCu(I)\cdot(t\text{-BuNC})}$$

solid, which is soluble in acetonitrile and hot benzene, and air sensitive. **3** could be purified by recrystallization from hot benzene under nitrogen. In the presence of an additional amount of *t*-BuNC, **3** is readily soluble in benzene even at room temperature. The elemental analysis, nmr, and ir were in accord with the structure of **3** (see Experimental Section). By a similar way, Cu(I) benzoate–*t*-BuNC complex was prepared.

3 reacted with alkyl halide even at room temperature to give the corresponding acetate. In the reaction of **3** with phenethyl bromide and chloride, phenethyl acetate was obtained in the yields of 88 and 12%, respectively. For the purpose of comparison, Cu(I) acetate prepared by Calvin's procedure[4,5] was also treated with alkyl halide. The results are summarized in Table I. Here it is seen that the isonitrile ligand enhances the reactivity of Cu(I) carboxylate toward alkyl halide.

Reaction of Cu(I) Acetate–*t*-BuNC Complex with (+)-(*R*)-Phenethyl Bromide.—The stereochemical course of the reaction of Cu(I) carboxylate–*t*-BuNC with alkyl halide was examined using an optically active halide, (+)-(*R*)-phenethyl bromide (**4**), having

$$CH_3COOCu(I)\cdot(t\text{-BuNC}) + (+)\text{-}(R)\text{-}\underset{\mathbf{4}}{C_6H_5\overset{Br}{\overset{|}{C}}HCH_3} \longrightarrow CH_3COO\overset{CH_3}{\overset{|}{\underset{H}{\underset{|}{C}}}}HC_6H_5 + CuBr\cdot(t\text{-BuNC}) \quad (3)$$

$[\alpha]^{25}D$ −41.6° (*c* 6.27, cyclohexane)

$[\alpha]^{25}D$ +58.6°. The optical purity of **4** employed in the present study was 45%.[6]

The reaction proceeded quantitatively (Table I). The product was purified by preparative glpc, which showed an optical rotation of $[\alpha]^{25}D$ −41.6° (Table I). The optical purity was calculated at 33% on the basis of the known rotation of optically pure phenethyl acetate.[7] As the authentic ester, (−)-(*S*)-phenethyl acetate was prepared by the reaction of (−)-(*S*)-phenethyl alcohol with acetic anhydride in pyridine, which was known to proceed with the retention of configuration.[7] It has been established that the bromination of alcohol using PBr_3 proceeds with the inversion of

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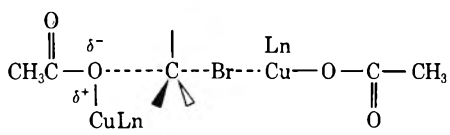
TABLE I
REACTION OF COPPER(I) ACETATE WITH PHENETHYL HALIDES

Copper acetates[f] (mmol)	Halides[f] (mmol)	Temp, °C	Time, hr	Product Yield, %	Product Optical activity $[\alpha]^{25}D$
$CH_3COOCu(I)$ (4.1) (598-54-9)	(±)-Phenethyl bromide (5)[b] (38661-81-3)	45	3	93	
$CH_3COOCu(I)$ (4.1)	(±)-Phenethyl bromide (2.4)[b]	r.t.[d]	2	52	
3 (8) (38641-29-1)	(±)-Phenethyl bromide (5)[a,c]	r.t.[d]	2	88	
3 (8)	(±)-Phenethyl chloride (5)[a,c] (38661-82-4)	r.t.[d]	2.5	12	
3 (8)	(±)-Phenethyl chloride (5)[a,c]	50	1	56	
$(CH_3COO)_2Cu(II)$ (5) (142-71-2)	(±)-Phenethyl bromide (5)[b]	45	3	Trace	
$CH_3COOCu(I)$ (3)	(+)-(*R*)-Phenethyl bromide (2.2)[b] (1459-14-9)	50	3	>90	−0.3° (*c* 6.62, cyclohexane)[e]
3 (4)	(+)-(*R*)-Phenethyl bromide (2.4)[b]	45	2	>90	−41.6° (*c* 6.27, cyclohexane)[e]

[a] The reaction was carried out in the presence of *tert*-butyl isocyanide (4 mmol). [b] Benzene (5 ml) was used as solvent. [c] Benzene (10 ml) was used as solvent. [d] r.t. = 18–20°. [e] Optical purity can be calculated on the optically pure phenethyl acetate[7] having $[\alpha]^{21}D$ −124.5 (c 3, benzene). [f] Registry numbers are in parentheses below compound.

configuration.[8,9] From these facts, it is concluded that the reaction (3) proceeds with a predominant stereochemistry of ~75% inversion of configuration. Next, Cu(I) acetate[4,5] having no isonitrile ligand was subjected to the reaction with optically active (+)-(*R*)-phenethyl bromide ($[\alpha]^{25}D$ +58.6°) under the designated conditions in Table I. In this case, the product, phenethyl acetate, has a very small rotation of $[\alpha]^{25}D$ −0.3°, indicating that this reaction proceeds with racemization. Here, it has become clear that the employment of isonitrile ligand in the reaction of Cu(I) carboxylate with alkyl halide greatly influences the stereochemistry of the reaction. Recently, Lewin[10] reported that the reaction of copper(I) carboxylate with alkyl halide in refluxing pyridine afforded ester with inversion. This is not inconsistent with our results, because pyridine as well as isonitrile are strongly coordinated ligands on copper. Perhaps the simplest mechanistic rationale of predominant inversion in reaction 3 is indicated in Scheme II. It may be supposed that the isonitrile ligand

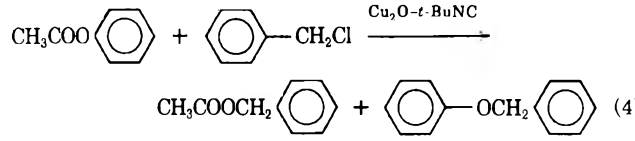
SCHEME II



Ln = ligand isonitrile

increases the nucleophilicity of carboxylate anion to cause a SN2 displacement.

In the course of our study, we found that the Cu_2O–isonitrile complex induced the ester interchange reaction between ester and alkyl halide, being accompanied with the formation of ether as formulated by eq 4. For example, a mixture of phenyl acetate and benzyl chloride was heated in benzene at 80° for 12 hr in the presence of Cu_2O–*t*-BuNC. The products were benzyl acetate and benzyl phenyl ether (eq 4). By glpc analysis, no other species, except for the starting two compounds, was detected in the reaction mixture.

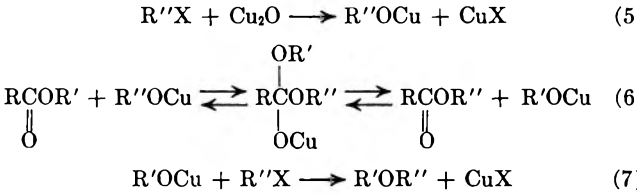


(4)

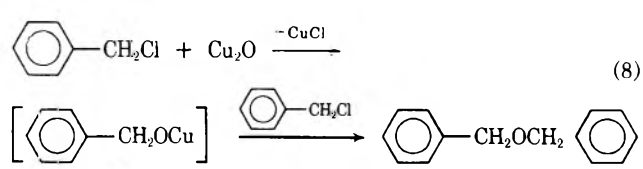
Other examples of the ester interchange reaction (*i.e.*, phenyl acetate–*n*-butyl bromide and benzyl benzoate–*n*-butyl bromide) are shown in Table II. The two alkyl groups of the product ether are derived from alkyl halide and ester.

From the material balance, one oxygen atom of Cu_2O is to be transferred to one of the products. The following (Scheme III) may be assumed. The reaction is initiated by the reaction of alkyl halide and Cu_2O to form Cu(I) alkoxide (eq 5). Then Cu(I) alkoxide may act as the key intermediate in the following manner. The isonitrile ligand is being omitted in this equation. The transient formation of Cu(I) alkoxide has been supported by a reference experiment in which a mixture of benzyl chloride (20 mmol), Cu_2O (10 mmol), and *t*-BuNC (20 mmol) at 80° for 12 hr produced benzyl ether in a yield of 51% on the basis of benzyl chloride. In this reaction, the transient formation of Cu(I) benzylate (**5**) will be assumed (eq 8).

SCHEME III



(5) (6) (7)



(8)

5

(8) W. Gerrard, *J. Chem. Soc.*, 848 (1945).
(9) D. G. Goodwin and H. R. Hudson, *J. Chem. Soc. B*, 1333 (1968).
(10) A. H. Lewin and N. L. Goldberg, *Tetrahedron Lett.*, 491 (1972).

TABLE II
REACTION OF ESTER WITH ALKYL HALIDE[a]

Ester[d] (mmol)	Halide[d] (mmol)	Cu_2O, mmol	t-BuNC, mmol	Time, hr	Product yield,[b] %
CH_3COOPh (10) (122-79-2)	$PhCH_2Cl$ (10) (100-44-7)	5	20	12	CH_3COOCH_2Ph 43[c] $PhOCH_2Ph$ 45[c]
CH_3COOPh (10)	n-BuBr (40) (109-65-9)	10	20	5	CH_3COO-n-Bu 40 PhO-n-Bu 41
$PhCOOCH_2Ph$ (10) (120-51-4)	n-BuBr (50)	10	15	8	PhCOO-n-Bu 38 $PhCH_2O$-n-Bu 36

[a] A mixture of ester with alkyl halide was heated at 80° in 10 ml of benzene under nitrogen. [b] Yield was determined by glpc analysis and calculated on the basis of ester. [c] Calculated on the basis of benzyl chloride. [d] Registry numbers are in parentheses.

In the two reactions of eq 5–7 and 8, a stoichiometric amount of Cu_2O is converted into Cu(I) halide. The formation of Cu(I) alkoxide requires alkyl halide.

Experimental Section

Materials.—Cu_2O and Cu(II) acetate were commercial reagents of analytical grade and were dried under nitrogen prior to use. Cu(I) acetate was prepared under nitrogen according to Calvin's method.[4,5] *tert*-Butyl isocyanide was prepared according to Ugi's procedure.[11] (−)-(*S*)-Phenethyl alcohol, $[\alpha]^{25}D$ −45.6° (*c* 3.29, cyclohexane) (lit. $[\alpha]^{23}D$ −45.5°),[12] was prepared according to Kenyon's method,[12] and was converted to (+)-(*R*)-phenethyl bromide, $[\alpha]^{25}D$ +58.6° (*c* 3.94, cyclohexane) (lit. $[\alpha]^{22}D$ +130.96°)[8] (optical purity 45%), according to a published method of Gerrard.[8]

Preparation of 1:1 Complex of Cu(I) Acetate–*t*-BuNC (3).—All the reagents were carefully dried and distilled under nitrogen. Under nitrogen, a mixture of acetic acid (34 mmol), Cu_2O (17 mmol), and *t*-BuNC (34 mmol) was heated in 24 ml of benzene at 80° for 2.5 hr. During the reaction, the production of water was observed. After filtration, the filtrate was subjected to evaporation *in vacuo* (10 mm). Then 20 ml of benzene was added and recrystallization was carried out by warming the mixture up to 80°. This procedure was repeated three times. The white residue was dried *in vacuo* (2–3 mm) at 80° for 12 hr (**3**, 1.85 g, 53% on the basis of Cu_2O). **3** was sensitive to air. When **3** was exposed to air in solid state, it turned light blue gradually, and in benzene solution it turned greenish blue immediately. Cu(I) acetate–*t*-BuNC (**3**) had nmr (CD_3CN) τ 8.51 (singlet, CH_3– and *tert*-butyl protons at the same position); ir (KBr) 2169 (C≡N), 1585, 1560 (COO), 1410, 1235, 1210 cm^{-1} (*tert*-butyl group).

Anal. Calcd for $C_7H_{12}NO_2Cu$: C, 40.87; H, 5.88; N, 6.81; Cu, 30.98. Found: C, 40.83; H, 6.13; N, 6.80; Cu, 30.40.

Preparation of 1:1 Complex of Cu(I) Benzoate–*t*-BuNC Complex.—A similar procedure was carried out with benzoic acid. The 1:1 complex was obtained: nmr (CD_3CN) τ ~2.6 (5 H), 8.55 (9 H); ir (KBr) 3060 (phenyl), 2168 (C≡N), ~1600, 1570 cm^{-1} (COO and phenyl).

Reaction of 3 or Cu(I) Acetate with (+)-(*R*)-Phenethyl Bromide. A.—Under nitrogen, **3** (4 mmol) was mixed with *t*-BuNC (2 mmol) in 5 ml of benzene. The solution became clear by the addition of *t*-BuNC. To this mixture, (+)-(*R*)-phenethyl bromide (2.35 mmol) was added dropwise at room temperature. The reaction mixture was stirred for 30 min at room temperature. Then it was elevated up to 45° and allowed to react for 2 hr. After the reaction, 30 ml of *n*-pentane was added to remove Cu-Br–*t*-BuNC by filtration. The filtrate was condensed at room temperature by evaporation *in vacuo* (10 mm). Analysis by glpc showed that the reaction was quantitative. The product ester was purified by preparative glpc. The specific rotation of the ester was $[\alpha]^{25}D$ −41.6° (*c* 6.27, cyclohexane), being opposite in sign to the original halide. This sign was the same as that obtained from the reaction of (−) alcohol with acetic acid anhydride.[7]

B.—The reaction of Cu(I) acetate with (+)-(*R*)-phenethyl bromide was carried out at 50° for 3 hr by a similar procedure. Yield of the ester was over 90%. The specific rotation of the product ester was $[\alpha]^{26}D$ −0.3° and $[\alpha]^{25}_{350}$ −1.5° (*c* 6.62, cyclohexane). By a reference experiment, it was confirmed that the optical active ester obtained in the above reaction (A) was not racemized under the reaction conditions.

Reaction of Ester with Alkyl Halide by Cu_2O–*t*-BuNC.—A typical procedure is as follows. Under nitrogen, a mixture of Cu_2O (5 mmol), phenyl acetate (10 mmol), and *t*-BuNC (20 mmol) in benzene was stirred at 80° for 5 min, and then benzyl chloride (10 mmol) was added dropwise and heated for 12 hr. Then 20 ml of petroleum ether was poured into the cooled reaction mixture. The precipitated CuCl–*t*-BuNC and some unreacted Cu_2O were removed by filtration. The yields of products were determined by glpc analysis of the filtrate. Benzyl acetate and benzyl phenyl ether were obtained in the yield of 42.5 and 44.5%, respectively. Dibenzyl ether was not detected in the reaction mixture. The product structures were determined by comparison of nmr and ir with those of the authentic sample.

Reaction of Benzyl Chloride by Cu_2O–*t*-BuNC.—Under nitrogen, a mixture of benzyl chloride (20 mmol), Cu_2O (10 mmol), and *t*-BuNC (20 mmol) was heated at 80° for 12 hr. *n*-Pentane was added to remove CuCl–*t*-BuNC and the unreacted Cu_2O by filtration. The yield of product was determined by glpc analysis of filtrate. Dibenzyl ether was obtained in a yield of 51% (on the basis of Cu_2O).

Registry No.—Acetic acid, 64-19-7; Cu_2O, 1317-39-1; *t*-BuNC, 7188-38-7; benzoic acid, 65-85-0; Cu(I) benzoate–*tert*-butyl isocyanide complex, 38641-30-4; benzyl ether, 103-50-4.

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(12) A. J. H. Houssa and J. Kenyon, *J. Chem. Soc.*, 2260 (1930).

Nucleophilic Methanolysis of 1-Acetyltetracyclo[3.2.0.0^{2,7}.0^{4,6}]heptane (2-Acetylquadricyclene) and Methyl 1-Tetracyclo[3.2.0.0^{2,7}.0^{4,6}]heptane carboxylate (2-Carbomethoxyquadricyclene)

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Although electrophilic additions to saturated, strained carbocyclic systems are commonplace, the corresponding nucleophilic additions are rare. Thus, such reactions as the alcoholysis of strained carbon linkages are usually feasible only in the presence of electrophilic catalysts (*e.g.*, H^+, Ag^+, etc.). We wish to report, however, that α-carbanion stabilizing substituents, such as the acetyl group, render the quadricyclene skeleton exceedingly reactive toward methanolysis not only under basic conditions but even in neutral solvent.

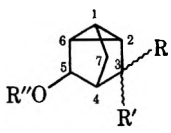
2-Acetylquadricyclene (**1a**), previously unreported, was prepared in nearly quantitative yield by sensitized

irradiation of 2-acetybicyclo[2.2.1]heptadiene (**2a**),[1] and characterized by its elemental composition, spectra, and Pd(II)-catalyzed cycloreversion to **2a**. When **1a** was treated with absolute methanol, a rapid, exothermic reaction ensued. Subsequent removal of excess solvent left crude 3-acetyl-5-methoxynortricyclene (**3a**, 95%) as a mixture (*ca.* 50:50) of C-3 epimers. The structure assigned to **3a** was inferred from its spectral and analytical data. In particular, the nmr spectrum exhibits two acetyl proton singlets at τ 7.87 and 7.93, one for each epimer, and two methoxy proton singlets at 6.77 and 6.79. The near-infrared spectrum of **3a** between 1.6 and 1.8 μ, the first C–H stretching vibration overtone region, closely resembles the published spectrum of parent nortricyclene,[2] while the infrared spectrum shows characteristic nortricyclene skeletal absorption at 12.35 μ.[3a-c]

The assignment of C-3 rather than C-5 as the epimeric carbon atom was confirmed by treatment of *ca.* 50:50 *exo*:*endo*-**3a** with sodium methoxide in methanol-*O*-*d*. All hydrogen atoms α to the carbonyl function, including H-3, underwent complete deuterium exchange, while the epimers of the resulting tetradeuteriononortricyclene **3b** were simultaneously equilibrated to a 35:65 ratio. No new isomers of **3b** were detected by nmr analysis. Had **3a** been epimeric at C-5 and of a single configuration (*i.e.*, exo or endo) at C-3, two additional isomers should have formed upon treatment with base.

1a, R = $COCH_3$
b, R = $COOCH_3$
c, R = $SO_2C_6H_5$

2a, R = $COCH_3$
b, R = $COOCH_3$

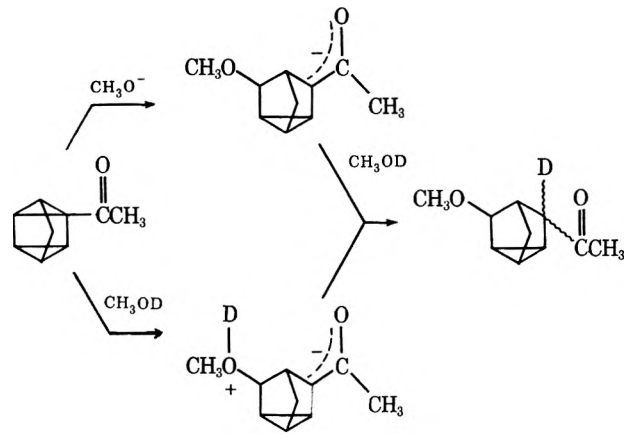


3

3	R	R′	R″
a	$COCH_3$	H	CH_3
b	$COCH_3$	D	CD_3
c	$COCH_3$	D	CH_3
d	CO_2CH_3	H	CH_3
e	$SO_2C_6H_5$	H	$C(CH_3)_3$

When quadricyclene **1a** was allowed to react with methanol-*O*-*d*, an 87% yield of crude 3-deuterio-3-acetyl-5-methoxynortricyclene (**3c**) was obtained. The position of the deuterium atom was fixed by the absence of a one-proton multiplet at τ 7.49 in its nmr spectrum. Preliminary nmr rate studies showed methoxide ion to be an active catalyst. Thus, the deuteriomethanolysis of 1.87 *M* **1a** was complete within 42 min at probe temperature (*ca.* 30°) in neutral solvent but required no more than 6 min to go to completion in the presence of 10 mol % sodium methoxide. In one experiment, addition of 1.95 *M* sodium methoxide in methanol to neat quadricyclyl methyl ketone initiated a near explosion.

It seems likely that the methanolysis of **1a** proceeds as depicted below. Catalysis by methoxide ion is consistent with rate-determining nucleophilic cleavage of the cyclopropane ring bonded to the acetyl function. Also, protonation of the indicated intermediates would be expected to afford epimeric C-3 product.



The reactivity of cyclopropanes toward nucleophilic addition is clearly enhanced by internal strain. Truce and Linday found, for example, that cyclopropyl methyl ketone had incompletely reacted with sodium thiophenoxide after 3 hr in refluxing ethanol.[4] However, electronic factors are also important. Indeed, 2-carbomethoxyquadricyclene (**1b**)[5] is significantly less reactive than **1a** toward nucleophilic alcoholysis.

When **1b** was allowed to stand in absolute methanol for nearly 7 days at room temperature, there was no reaction. After 4 days in refluxing methanol, **1b** was partially isomerized to diene **2b** (14%) and largely converted to 3-carbomethoxy-5-methoxynortricyclene (**3d**, 72%). Methoxide ion effectively catalyzes the addition of methanol to **1b**. In one experiment, **1b** and sodium methoxide (110 mol %) were mixed in methanol at room temperature. After 5 days, the reaction mixture was poured into water and extracted with dichloromethane. Ultimately, a 47:53 mixture of 3-*exo*,*endo*-carbomethoxy-5-*exo*-methoxynortricyclene (**3d**) was obtained in 72% yield. The structure assigned to **3d** was based on spectral comparison (ir, near-ir, nmr) with authentic material prepared by the action of sulfuric acid on methanolic **1b** and confirmed by comparison of chemical shift parameters to those published[3c] for known *exo*- and *endo*-**3d**.

The facility with which **1a** and **1b** add methanol contrasts with the severe conditions often necessary to promote nucleophilic additions to appropriately substituted, strained carbocycles.[4,6a-d] We note, however, that *uncatalyzed*, room-temperature methanolyses of spiro[2.5]octa-4,7-dien-6-one[7] and the photobicyclobutane derived from $\Delta^{3,5}$-cholestadiene[8] have been

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(8) W. G. Dauben and F. G. Willey, *Tetrahedron Lett.*, 893 (1962).

reported. Also, 1-cyanobicyclo[1.1.0]butane[9] and 1-cyano-3-methylbicyclo[1.1.0]butane[6d] have been found to undergo methoxide-catalyzed addition of methanol at room temperature. The reactions of **1a** and **1b** described herein corroborate the earlier finding of Cristol and Singer that treatment of quadricyclyl phenyl sulfone (**1c**) with potassium *tert*-butoxide and *tert*-butyl alcohol in dimethyl sulfoxide gave, after 18 hr at room temperature, a 34% yield of 3-*exo*,*endo*-phenylsulfonyl-5-*exo*-*tert*-butoxynortricyclene (**3e**).[6d,10] Finally, the lesser reactivity of **1b** relative to **1a** must reflect the superior ability of the acetyl group over the carbomethoxy group to stabilize adjacent negative charge.

Experimental Section

General.—The photoisomerizations described herein were conducted in a Rayonet photochemical reactor equipped with 16 3500-Å lamps and an RQV-118 quartz reaction vessel. Nmr spectra were recorded on a Varian Model A-60 nmr spectrometer (relative to internal TMS), infrared spectra on a Perkin-Elmer Model 337 spectrophotometer, and near-infrared spectra on a Cary-17 uv-vis-ir spectrophotometer. Boiling points are uncorrected. Glpc analyses were performed on a Hewlett-Packard Model 5750 gas chromatograph, a 6-ft column of 10% UCON W-98 on 80–100 mesh silica being utilized. Elemental compositions were determined by Galbraith Laboratories, Inc., Knoxville, Tenn. Sodium methoxide was obtained from the J. T. Baker Chemical Co. and methanol-*O*-*d* (99%) from Diaprep Inc.

2-Acetylquadricyclene (1a).—A solution of diene **2a** (20.0 g, 149 mmol) and bis(dimethylamino)benzophenone (0.6 g, 2.2 mmol) in ether (125 ml) was irradiated for 28 hr. The solvent and sensitizer were subsequently removed and the crude product was distilled, giving 17.9 g (89%) of **1a** as a colorless liquid: bp 45–47° (0.5 mm); ir (neat) 3.25 (cyclopropyl CH), 6.02 μ (C=O); nmr (CD_3COCD_3) τ 7.30–7.65 (m, 2), 7.8–8.1 (m, 3), 8.21 (s, 3, $COCH_3$), 8.25–8.45 (m, 2).

Anal. Calcd for $C_9H_{10}O$: C, 80.60; H, 7.46. Found: C, 80.50; H, 7.46.

A 0.3-g sample of the presumed quadricyclene (from a benzophenone-sensitized run) was dissolved in chloroform-*d* (0.5 ml) and treated with bis(benzonitrile)palladium(II) chloride (0.025 g). An nmr spectrum recorded shortly thereafter was, except for minor impurities, identical with that of diene **2a**.

Under ambient conditions, 1a rapidly becomes colored and is eventually transformed into a red gum. It can, however, be stored for long periods at low temperatures.

Methanolysis of 1a.—To 7.58 g (56 mmol) of **1a** was added 10 ml of absolute methanol. Within several minutes, there was heat evolution sufficient to cause the solvent to reflux. After 19 hr, the excess methanol was evaporated *in vacuo*, leaving 8.85 g (95%) of crude **3a** as a yellow oil which was then distilled to a colorless liquid: bp 50.5–53.5° (0.05–0.07 mm); ir (neat) 3.27 (cyclopropyl CH), 5.86 (C=O), 9.05 (COC), 12.35 μ (nortricyclene skeleton); near-ir (CCl_4) λ_{max} 1.659 μ (ϵ 1.233) (first CH stretching vibration overtone characteristic of the nortricyclene skeleton); nmr (CD_3COCD_3) τ 7.87 and 7.93 (singlets, O=C-CH_3), 7.68 (m, H-4), 7.49 (m, H-3), 6.77 and 6.79 (singlets, OCH_3), 6.55 (broad singlet, H-5), 8.0–9.1 (complex multiplets, H-1,2,6,7,7′). The acetyl proton singlets are of nearly equal intensity, as are the methoxy proton singlets, consistent with the formulation of **3a** as an equimolar mixture of C-3 epimers.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.02; H, 8.52.

Deuteriomethanolysis of 1a.—Quadricyclene **1a** (1.34 g, 10 mmol) was dissolved in methanol-*O*-*d* (10 ml) and stirred at room temperature for *ca.* 22 hr. Vacuum evaporation of the solvent left 1.45 g (87%) of crude deuterionortricyclene (**3c**) as a clear, yellow oil: ir (neat) 3.26 (cyclopropyl CH), 5.87 (C=O), 9.05 (COC), 12.26 μ (nortricyclene skeleton); nmr (CD_3COCD_3) τ 7.87 and 7.93 (*ca.* 1:1 singlets, O=CCH_3), 7.72 (m, H-4), 6.77 and 6.80 (*ca.* 1:1 singlets, OCH_3), 6.55 (broad singlet, H-5), 8.0–9.1 (complex multiplets, H-1,2,6,7,7′). Except for the absence of a one-proton multiplet at τ 7.49 (H-3), the nmr spectrum of **3c** is nearly identical with that of **3a**.

Methoxide-Catalyzed Epimerization and α-Hydrogen Exchange in 3a.—To 1.67 g (10 mmol) of *ca.* 50:50 *exo*:*endo*-**3a** was added 10 ml of 0.16 *M* sodium methoxide in methanol-*O*-*d*. After stirring at room temperature for *ca.* 2.35 hr, the reaction mixture was poured into 50 ml of water and extracted with three 100-ml portions of dichloromethane. The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*, leaving 1.50 g (88%) of tetradeuterionortricyclene (**3b**) as a clear, colorless liquid: ir (neat) 3.27 (cyclopropyl CH), 5.89 (C=O), 9.04 (COC), 12.3 μ (nortricyclene skeleton). Except for the absence of singlets at τ 7.87 and 7.93 (O=CCH_3) and a multiplet at τ 7.49 (H-3), the nmr spectrum of **3b** is nearly identical with that of **3a**. However, the methoxy resonances at τ 6.77 and 6.79 are no longer of equal intensity but are in a 65:35 ratio.

Preliminary Rate Studies.—The deuteriomethanolysis of quadricyclene **1a** was followed by nmr spectroscopy at instrument probe temperature (*ca.* 30°). Owing to the large solvent proton resonance ($\sim\tau$ 6.7), the spectral region between τ 7.5 and 10.0 was isolated for analysis.

A. Uncatalyzed.—Three 50-μl portions of **1a** (164 mg, 1.22 mmol) were injected into methanol-*O*-*d* (0.5 ml), and nmr spectra were recorded *ca.* 7, 16, 26, 40, and 49 min after the time of mixing. Reaction progress was monitored by the disappearance of the acetyl singlet of **1a** and the appearance of the acetyl singlets of **3c**. The conversion of **1a** to **3c** was more than 70% complete within 7–8 min and 100% complete within 40 min.

B. Catalyzed.—Three 50-μl portions of **1a** were injected into 0.5 ml of 0.25 *M* sodium methoxide in methanol-*O*-*d*. By the time an nmr spectrum was recorded (within 4–7 min from the time of mixing), the alcoholysis of **1a** was complete. The spectrum of the reaction mixture was identical with that of tetradeuterionortricyclene **3b**.

2-Carbomethoxyquadricyclene (1b).—Although the synthesis of 1b has appeared in the literature,[5] preparative details and spectral parameters were not described. Thus, we include herein our synthesis and characterization of **1b**.

A solution of diene **2b** (20.0 g, 133 mmol) and bis(dimethylamino)benzophenone (0.6 g, 2.2 mmol) in ether (125 ml) was irradiated for 24 hr. Removal of the solvent and sensitizer and distillation of the crude product gave 16.6 g (83%) of **1b** as a clear, colorless liquid: bp 40–42° (0.5 mm); ir (neat) 3.28 (cyclopropyl CH), 5.83 μ (C=O); nmr (CD_3COCD_3) τ 6.44 (s, $COOCH_3$), 7.58 (complex multiplet, 7).

Anal. Calcd for $C_9H_{10}O_2$: C, 72.00; H, 6.67. Found: C, 71.97; H, 6.85.

When 0.3-g samples of neat **1b** were heated at *ca.* 103° (oil bath), isomerization to diene **2b** was effected (as determined by nmr analysis).

Reaction time, hr	Approximate mole ratio **1b**:**2b**
21	50:50
24	54:46
24	46:54
25	52:48

Acid-Catalyzed Methanolysis of 1b.—A solution of 1b (7.50 g, 50 mmol) in methanol (40 ml) was treated with 1 ml of concentrated sulfuric acid. After several hours, the reaction mixture was poured into dichloromethane (200 ml), washed with two 50-ml portions of saturated aqueous sodium bicarbonate and two 50-ml portions of water, dried ($MgSO_4$), and concentrated at reduced pressure. Distillation of the crude product gave 6.74 g (74%) of 3-*exo*,*endo*-carbomethoxy-5-*exo*-methoxynortricyclene (**3d**): bp 70–72° (0.5 mm) [lit.[3c] bp 60° (0.3 mm)]; ir (neat) 5.77 (C=O), 12.3 μ (nortricyclene skeleton); near-ir (CCl_4) λ_{max} 1.658 μ (ϵ 1.312) (nortricyclene skeleton, first CH stretching vibration overtone); nmr (CD_3COCD_3) τ 6.37 (s, $COOCH_3$ of *endo*-**3d**), 6.41 (s, $COOCH_3$ of *exo*-**3d**), 6.58 (m, H-5 of *exo*-**3d**), 6.78 (s, $-OCH_3$ of *exo*- and *endo*-**3d**), 7.65–8.90 (several complex multiplets, H-1,2,4,6,7,7′ of *exo*- and *endo*-**3d** (the H-5 resonance of *endo*-**3d** is buried under the 6.37 singlet); glpc 65:35 *endo*:*exo*-**3d**.

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.93; H, 7.69. Found: C, 66.48; H, 7.47.

Methoxide-Catalyzed Methanolysis of 1b.—A solution of **1b** (1.50 g, 10 mmol) in methanol (5 ml) and a solution of sodium methoxide (0.54 g, 10 mmol) in methanol (5 ml) were mixed and allowed to stir for 5 days at room temperature. The reaction

(9) H. K. Hall, Jr., E. P. Blanchard, Jr., S. C. Cherkofsky, J. B. Sieja, and W. A. Sheppard, *J. Amer. Chem. Soc.*, **93**, 110 (1971).

(10) M. S. Singer, Ph.D. Thesis, University of Colorado, 1966, pp 71–73.

mixture was then poured into water (100 ml) and extracted with three portions (100 ml each) of dichloromethane. The combined extracts were dried ($MgSO_4$) and concentrated at reduced pressure, leaving 1.32 g (72%) of a clear oil with spectra (ir, near ir, nmr) identical with those described for authentic 5-*exo*-methoxy-3-*exo*,*endo*-carbomethoxynortricyclene (**3d**): glpc 47:53 endo:exo.

In a control experiment, a solution of **1b** (1.53 g, 10 mmol) in methanol (10 ml) was allowed to stir at room temperature for nearly 7 days. Vacuum evaporation of the solvent left 1.45 g (95%) of product with an nmr spectrum identical with that of unreacted starting material.

Uncatalyzed Methanolysis of 1b.—A solution of **1b** (1.50 g, 10 mmol) in methanol (10 ml) was refluxed mildly over a period of 4 days. Reduced pressure evaporation of the solvent left 1.61 g of crude product found by nmr analysis to consist primarily of diene **2b** (14%), nortricyclene **3d** (72%), and unreacted **1b** (13%). The product ratios were estimated by integration of appropriate carbomethoxy proton resonances. However, owing to significant peak overlap, they may be somewhat in error.

Registry No.—**1a**, 38739-89-8; **1b**, 24161-47-5; **2a**, 38739-91-2; **2b**, 3604-36-2; *endo*-**3a**, 38739-93-4; *exo*-**3a**, 38822-43-4; *endo*-**3b**, 38822-44-5; *exo*-**3b**, 38822-45-6; *endo*-**3c**, 38822-46-7; *exo*-**3c**, 38734-70-2; *endo*-**3d**, 28298-03-5; *exo*-**3d**, 35193-30-7; bis(dimethylamino)benzophenone, 90-94-8.

Synthesis of Cyclodec-3-en-1-ols by Acid-Catalyzed Two-Carbon Ring Expansion

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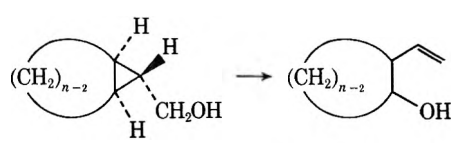
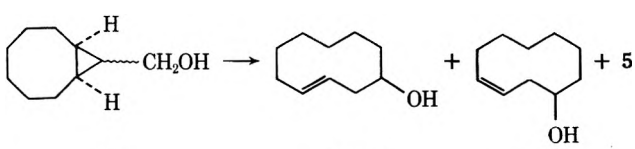
Acid-catalyzed rearrangement of bicyclo[*n*.1.0]alkyl methanols (**1**) represents an effective synthetic route to 2-vinylcycloalkanols (**2**) for certain ring sizes.[1]



1 **2**

$n = 4, 5, 6$

In an effort to use this reaction with an eight-membered ring (**3**), we discovered that the major products



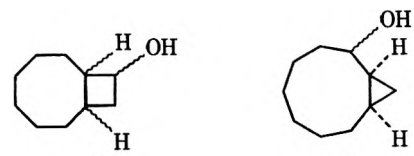
3 *trans*-**4** *cis*-**4**

of the reaction are not analogous to **2** but rather are the result of an interesting two-carbon ring expansion.[2,3] The rearrangement provides a convenient synthetic route to 3-cyclodecenols.

Compound **3** is readily prepared from cyclooctene by addition of ethyl diazoacetate followed by hydride reduction. This results in a 66:34 mixture of exo and endo isomers. Acid-catalyzed rearrangement of the mixture gave a 74:19:7 ratio of *trans*-**4**, *cis*-**4**, and **5** in an overall yield of 95%. Products *cis*-**4** and *trans*-**4** were identified by retention time comparisons of the alcohols and their trimethylsilyl derivatives and by spectral comparisons with authentic samples. The minor component (**5**) is an isomeric alcohol of unknown structure.

The isomers of **3** (*syn*-**3** and *anti*-**3**) were separated by gas chromatography and examined separately. Acid-catalyzed rearrangement of *anti*-**3** gave only the trans ring-expanded product, *trans*-**4**. Rearrangement of *syn*-**3** gave a 46:40:9:4 ratio of *trans*-**4**, *cis*-**4**, **5**, and another unknown compound.

No cyclobutanol products **6** were detected. A mixture of cyclobutanols (**6**) was prepared and coinjected



6 **7**

on gc and was found not to enhance any of the product peaks. It was also established that the cyclobutanols are stable to the acid catalysis conditions.

It should be noted that a stereospecific synthesis of *cis*-**4** or *trans*-**4** is best accomplished by the Winstein–Poulter method[4] involving stereospecific rearrangement of bicyclo[7.1.0]decan-2-ols, **7**. Although the syntheses of *cis*,*syn*- or *cis*,*anti*-**7** are lengthy, they are formed with high stereoselectivity and require no difficult separations. Although *anti*-**3** rearranges cleanly to *trans*-**4**, the synthesis of *anti*-**3** is nonselective and the separation is difficult.

The rearrangement of **3** is more useful where the stereochemistry of the double bond is not crucial, *e.g.*, in making compounds where the double bond is to be removed.[5] For those cases the sequence requires fewer steps than the Winstein–Poulter method and gives a higher overall yield (35% *vs.* 19%).

Experimental Section

Spectral measurements utilized Beckman IR-8, Varian Associates A-60 or HA-100, and Atlas CH7 instruments. Analyses were performed by Alfred Bernhardt Microanalytisches Laboratorium or Galbraith Laboratories, Analytical gas chromatography (gc) was carried out with a Wilkens Aerograph Model 1200 instrument with flame ionization detector and the 0.01-in. capillary columns listed: (A) 125 ft UCONLB550X, (B) 75 ft DEGS, (C) 100 ft Apiezon N. Samples were collected using an

(1) (a) T. L. Bond, *Tetrahedron Lett.*, 4255 (1965); (b) K. B. Wiberg and A. J. Ashe, *J. Amer. Chem. Soc.*, **90**, 63 (1968).

(2) Solvolysis of the analogous seven-membered ring dinitrobenzoate has recently been reported: K. B. Wiberg and T. Nakihara, *ibid.*, **93**, 5193 (1971).

(3) Unpublished work of E. Walton in these laboratories has shown that the analogous [5.1.0] bicyclic system does not give this two-carbon ring expansion. The syn (endo) isomers of the analogous [3.1.0] and [2.1.0] systems favor the ring expansion while the anti (exo) isomers show none of that process.[1a]

(4) S. Winstein and C. D. Poulter, *J. Amer. Chem. Soc.*, **92**, 4282 (1970), and references cited therein.

(5) Hydrogenation of the 3-cyclodecenols in ether over Adams catalyst is essentially quantitative (determined by internal glc standard).

Aerograph A90-P instrument using the 0.25-in. columns listed: (D) 10 ft, 5% KOH-5% Carbowax 4000 on Chromosorb W, (E) 10 ft, 5% UCONLB550X on Chromosorb G.

Preparation of the *cis*-Bicyclo[6.1.0]nonane-9-methanols (*syn*-3 and *anti*-3).—To 165 g (1.5 mol) of cyclooctene was added 4.0 g of anhydrous cupric sulfate. The mixture was heated and stirred at 70–80° under nitrogen while 28.5 g (0.25 mol) of ethyl diazoacetate[6] was added dropwise (*ca.* 1 hr for addition). The solution was heated and stirred at 55–60° overnight. The cupric sulfate was removed by filtration. Analysis by gc on column B at 110° showed essentially two volatile products in a ratio of 34:66.

To 140 ml of Vitride in 100 ml of dry ether was slowly added (*ca.* 2 hr) the crude reaction mixture at reflux. The mixture was allowed to cool to room temperature and stir overnight. To the crude reaction solution was added dropwise 100 ml of saturated sodium carbonate solution. The organic and aqueous layers were separated, and the organic layer was washed with two 50-ml portions of saturated sodium carbonate solution, four 50-ml portions of water, and one 50-ml portion of saturated salt solution. The organic layer was dried over anhydrous magnesium sulfate and filtered, and all of the volatile solvent was removed on a rotary evaporator. The crude, dark mixture was vacuum distilled to give 18.6 g (48.3%) of light yellow liquid, bp 96–100° (0.6 mm). Gc analysis on column C at 135° showed essentially two components in a ratio of 66:34 which were separated by gc using column D at 140°. Collection of the first component gave *anti*-3 (100% pure by gc): ir (neat) 3325, 3000, 2920, 2870, 1470, 1440, 1140, 1103, 1075, 1030, 1020 cm^{-1}; nmr (CCl_4, 100 MHz) δ 0.31–0.68 (m, 3), 0.75–2.23 (m, 13), 3.35 (d, J = 6 Hz, 2).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.88; H, 11.66. Found: C, 77.72; H, 11.88.

Collection of the second peak gave 35% *anti*-3 and 65% *syn*-3. A more effective separation was obtained by converting the 66:34 *syn*- and *anti*-3 mixture to trimethylsilyl ethers and separating the mixture on column E at 115°. Hydrolysis[7] of the second gc fraction gave *syn*-3 (still contained 12% *anti*-3): ir (neat) 3375, 3000, 2920, 2870, 1470, 1440, 1160, 1145, 1105, 1090, 1015 cm^{-1}; nmr (CCl_4, 100 MHz) δ 0.57–2.30 (m, 16), 3.57 (d, J = 7 Hz, 2).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.88; H, 11.66. Found: C, 77.68; H, 11.74.

The trimethylsilyl derivative was prepared by shaking for 10 min a mixture of 100 μl of **3**, 200 μl of Tri-sil,[8] and 400 μl of dimethyl sulfoxide. The mixture was extracted twice with 2-ml portions of pentane. The pentane solution was washed with 10% sulfuric acid and water and dried over sodium sulfate.

Acid-Catalyzed Rearrangement of *anti*-3.—To 0.11 g (0.73 mmol) of *anti*-3 was added 0.84 ml of 0.23 M perchloric acid and 4 ml of dioxane. The mixture was heated and stirred at 80° for 15 hr, whereupon all of the starting material was shown to be gone by gc on column C. To the mixture was added 30 ml of ether. The ether solution was washed with two 20-ml portions of 10% sodium carbonate, one 20-ml portion of water, and one 20-ml portion of saturated salt solution. The organic layer was dried over anhydrous magnesium sulfate and filtered, and the ether was removed on a rotary evaporator to yield 0.10 g (95%) of clear, viscous 4 (>95% pure on column C at 135°): ir (neat) 3320, 2900, 2700, 1450, 1350, 1260, 1170, 1120, 1053, 1015, 985, 860, 705 cm^{-1}; nmr (CCl_4, 100 MHz) δ 1.06–1.83 (m, 10), 1.83–2.28 (m, 3), 2.32–2.69 (m, 1), 3.21 (OH, 1), 3.73, (m, 1), 5.45 (m, 2). The ir and nmr spectra of an authentic sample of *trans*-cyclodec-3-en-1-ol and those of the major component were identical.

Further gc analysis was conducted on the trimethylsilyl ether of the reaction product (prepared as above). Analysis by gc on column A at 130° showed essentially one peak (>98%, 6.8 min). Coinjection of this major component with the trimethylsilyl derivative of *trans*-cyclodec-3-en-1-ol on two different columns gave one peak. The minor component (<2%, 10.0 min) was shown not to be the trimethylsilyl ether of *cis*-cyclodec-3-en-1-ol by coinjection with an authentic sample.

Acid-Catalyzed Rearrangement of *syn*-3.—A solution of 0.011 g of *syn*-3 (containing 12% *anti*-3), 2 ml of dioxane, and 84 μl of 0.23 M perchloric acid was heated at 80–85° for 20.5 hr and then worked up as described above. A portion of the reaction products was converted to trimethylsilyl derivative (as above) and analyzed on column A at 130° which showed four products in a ratio of 9:4:46:40. The latter two components were shown to be *trans*-4 and *cis*-4, respectively, by coinjection on columns A and C with authentic samples and by mass spectral comparison with these samples.

Acid-Catalyzed Rearrangement of a Mixture of *syn*-3 and *anti*-3.—To 6.5 g (0.042 mol) of **3** (66:34 mixture of *anti*-3 and *syn*-3) was added 220 ml of dioxane, 48 ml of water, and 1.6 g of 70% perchloric acid. The mixture was stirred, heated for 12 hr at 85–90°, and worked up as described above, which gave 6.2 g (95%) of products. A portion was converted to the trimethylsilyl derivative (as above) and analyzed on column A at 130° which gave four peaks in a ratio of 6:64:16:14. The first peak corresponds to the 9% unknown component observed from rearrangement of *syn*-3. The next two peaks correspond to *trans*-4 and *cis*-4; the last peak is unreacted *syn*-3 (coinjection on column A and C and mass spectral comparison).

Bicyclo[6.2.0]decan-9-ols (6).—The method of Wiberg and Nakihara[2] was used to produce bicyclo[6.2.0]decan-9-one (C=O at 1760 cm^{-1}), which was reduced with lithium aluminum hydride to give a mixture of alcohols (6): ir (neat) 3430, 2980, 2860, 1465, 1440, 1325, 1190, 1135, 1095, 1065, 870, 810 cm^{-1}; nmr (CCl_4, 100 MHz) δ 1.07–2.10 (m, 16), 3.23–4.02 (m, 1), 4.93 (s, OH).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.88; H, 11.66. Found: C, 77.78; H, 11.82.

Analysis of the trimethylsilyl derivative of the above mixture (column A) indicated four overlapping peaks in an approximate ratio of 5:50:40:5. Coinjection of this mixture with the trimethylsilylated mixture from 3 gave no enhancement of peaks.

Registry No.—*syn*-3, 38858-51-4; *anti*-3, 38858-52-5; *trans*-4, 29971-50-4; *cis*-4, 29746-36-9; 6, 38868-39-2; cyclooctene, 931-88-4; bicyclo[6.2.0]decan-9-one, 38868-40-5.

Acknowledgment.—We thank the Research Corporation for their support of this work.

(6) E. B. Womack and A. G. Nelson, "Organic Syntheses," Collect. Vol III, Wiley, New York, N. Y., 1955, p 392.

(7) S. Friedman and M. L. Kaufman, *Anal. Chem.*, **38**, 144 (1966).

(8) Pierce Chemical Co.

Christinine, a New Epoxyguaianolide from *Stevia Serrata* Cav.

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Contribution No. 367 from the Instituto de Química de la Universidad Nacional Autónoma de México, México 20, D. F.

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Very few sesquiterpene lactones had been isolated from *Stevia* genera.[1] We now describe the structure determination of a new guaianolide from *Stevia serrata* Cav.[2] which we have named *christinine*.

Fractionation of the methanol extract with chloroform and chromatographic separation involving silica gel and alumina yielded christinine ($C_{19}H_{24}O_7$).[3] The ion m/e 304 [M^+ − (CH_3COOH)] was observed by mass spectrometry: mp 164–165°; $[\alpha]D$ + 19.72° (c 3.65, $CHCl_3$); uv max (95% EtOH) 215 nm (ϵ 2270); ir ($CHCl_3$) 1775 (lactone), 1730 cm^{-1} (acetate).

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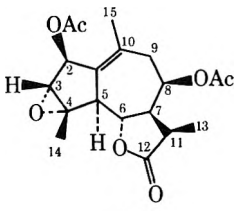
(1) T. Ríos, A. Romo de Vivar, and J. Romo, *Tetrahedron*, **23**, 4265 (1967).

(2) We are indebted to Mr. H. Quero-Rico from the Instituto de Biología, UNAM, for the classification of the plant.

(3) Cited empirical formula was supported by satisfactory analysis and/or mass spectral molecular weight. We thank Mr. Cortés for the mass spectral data.

The proposed structure and stereochemistry of christinine (1) are based on the evidence gained from



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the chemical shifts and coupling constants of its HA-100 nmr spectra (Table I) and verified by spin-decoupling experiments. Confirmations of the various assignments and pertinent coupling constants were sought using $Eu(DPM)_3$ as a chemical shift reagent.

TABLE I

NMR DATA FOR CHRISTININE

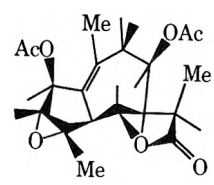
Proton	Multiplicity	Chemical shifts[a] C_6D_6	Chemical shifts[a] $CDCl_3$	Coupling constants
H_2	c	5.58	5.82	$J_{2,3} = 2.0$
				$J_{2,5} = 1.0$
				$J_{2,9} = J_{2,9'} = 1.75$
				$J_{2,15} = 1.75$
H_8	ddd	4.73	5.29	$J_{8,7} = 1.5$
				$J_{8,9} = 6.0$
				$J_{8,9'} = 1.5$
H_6	dd	3.72	4.3	$J_{6,5} = 10$
				$J_{6,7} = 9.5$
H_3	dd	3.45	3.64	$J_{3,5} = 1.0$
H_5	br d	2.74	3.17	$J_{5,15} = 1.75$
H_{11}	quintet	2.13	2.74	$J_{11,13} = 7.5$
H_7	ddd	2.25	2.58	$J_{7,11} = 7.0$
OAc	s	1.69	2.11	
OAc	s	1.57	2.01	
H_{14}	s	1.55	1.62	
H_{15}	t	1.41	1.61	
H_{13}	d	0.86	1.16	
H_9[b]	dd	4.7		$J_{9,8} = 7$; $J_{9,9'} = 15$
H_9[b]	br d	3.4		$J_{9',8} = 2$
OAc in C_2[b]	s	5.86		
OAc in C_8[b]	s	3.46		

[a] Chemical shifts are given in parts per million (δ scale) relative to TMS as internal standard. The coupling constants are in hertz. Singlets are marked as s. Multiplets are described as follows: d = doublet, t = triplet, br = broad, c = complex signal whose center is given. [b] Assignments of these signals were made using 30 mg of $Eu(DPM)_3$.

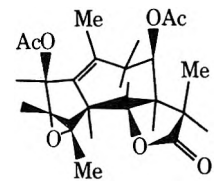
The trans diaxial positions between protons H_5 and H_6 and H_6 and H_7 were assigned based on $J_{5,6}$ and $J_{6,7}$ values, confirming firmly the trans ring attachment of the γ-lactone, H_5 and H_7 being α as has been proposed for globicin,[4] achillin,[5] and hydroxyachillin.[6] Decoupling of the methyl doublet at 1.16 ppm caused the quintet at 2.74 ppm corresponding to H_{11} to collapse to a doublet ($J_{7,11} = 7$ Hz). Quintets with these characteristics have been observed[6,7] in compounds with the stereochemistry of H_{11} α and a dihedral angle H_{11}–H_7 of *ca.* 30°.

A small long-range 4σ coupling between the allylic protons H_5 and H_2 was observed. This fact can only be made plausible when the two protons are α and a *M* or *W* coupling exists between them.[8] Irradiation of the C_{15} methyl signal at 1.61 ppm caused the multiplet at 5.82 ppm (assigned to H_2) to collapse, producing a quartet. Finally, triple irradiation at 1.61 and 3.17 ppm (attributed to H_5) eliminated the homoallylic and the 4σ coupling at 5.82 ppm, giving a triplet, suggesting similar angles for the homoallylic interaction,[9] H_2 with H_9 and $H_{9'}$, $J_{2,9} = J_{2,9'} = 1.75$ Hz. This demonstrates that the eliminated second coupling constant, $J = 1.0$ Hz, was caused by the *M* interaction between H_2 and H_5, possible only when these protons are in the *M* path. Another confirming fact that H_2 is in the α position is the dihedral angle of about 60° between H_2 and H_3,[10] resulting from the largest coupling constant, $J_{2,3} = 2.0$ Hz, thus establishing H_3 as β leaving the 3,4 epoxide in the α position as has been proposed by Kupchan and coworkers in a series of α-3,4-epoxy lactones.[11]

The stereochemistry of the C_8 acetate could be α or β and each isomer could exist in two conformations, these being the chair and boat forms of the seven-membered ring. One can eliminate the two conformations for the acetate in the α position because the coupling constant $J_{7,8}$ in the chair conformation should be larger. This has been observed in hydroxyachillin.[6] In case of a boat conformer, the signal for the homoallylic interaction of H_2 with H_9 and $H_{9'}$ would be a triplet, and not a quartet, as observed by irradiation of the C_{15} proton signals. From the other two possible conformations structure **1a** can be eliminated for the



1a



1b

following reasons. H_7 and H_8 should be in an α position with a dihedral angle of 15° and would show a larger coupling constant between them. In addition, the quartet for H_2 at 5.82 ppm formed by the homoallylic interactions with H_9 and H_9' would not be observable for this conformation. According to these results, we conclude that christinine must have the conformational structure **1b**.

Experimental Section

The uncorrected melting point was determined on a Culatti capillary melting point apparatus.

Infrared Spectra.—A Perkin-Elmer Model 521 infrared spectrophotometer was used. The sample was run in chloroform.

Optical Rotation.—A Perkin-Elmer Model 141 polarimeter was used.

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(9) Reference 8, p 110.

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Mass Spectra.—An Hitachi Perkin-Elmer RMU-6D double focussing mass spectrometer was used, operating at 75 eV, with an inlet and source temperature of *ca.* 215°.

Nuclear Magnetic Resonance Spectra.—A Varian HA-100 spectrometer with Hewlett-Packard audio oscillator Models 200 CD and 200 AB was used. The samples were run in benzene-d_6 and deuterio chloroform, with tetramethylsilane as internal standard.

Isolation Procedure.—*Stevia serrata* was collected in September 1971 south of México City. A 4-kg portion of dried whole plant was extracted with 25 l. of warm methanol. The extract was filtered and concentrated to 2 l., then 1 l. of water was added and extracted, first with 1 l. of hexane, which was discarded, and then with 2 l. of chloroform. The chloroform extract was washed with water and concentrated to dryness, giving 200 g of a syrupy brown oil. The part soluble in AcOEt 10/B90, 180 g, was chromatographed on silica gel (packed in AcOEt 10/B90). The column was successively eluted, starting with 3 l. of AcOEt 10/B90, and increasing the amount of AcOEt in the solvent mixture in the following fashion: 3 l. (40/60), 4 l. (60/40), 2 l. (100); fractions close to 300 ml were taken. Fractions 20–40 were combined and evaporated to dryness, and the residue, 123 g of syrup, was redissolved in AcOEt 5/B95 and chromatographed in 2 kg of alumina. The column was packed in AcOEt 5/B95 and successively eluted, taking fractions of about 500 ml, first 5 l. (AcOEt 5/B95), 5 l. (AcOEt 10/B90), 20 l. (AcOEt 20/B80), 7 l. (AcOEt 40/B60), and finally 2 l. (AcOEt 90/MeOH 10). All fractions were monitored by tlc. Fractions 32–37 were joined and christinine, 250 mg, crystallized out in ethyl acetate–hexane. One recrystallization from acetone–diisopropyl ether yielded pure christinine (1): mp 164–165°; $[\alpha]D$ + 19.72° (*c* 3.65, $CHCl_3$); ir ($CHCl_3$) 1775, 1730, 1360, 1000, 940 cm^{-1}; uv max (95% EtOH) 215 nm (ϵ 2270); mass spectrum (75 eV) *m/e* (rel intensity) 304 (M^+ − 60), 244 (45), 202 (64), 200 (74), 185 (47), 171 (77), 159 (100), 157 (63), 141 (70), 131 (85), 129 (77), 128 (82), 115 (71), 105 (24), 91 (39), 60 (31), 45 (20), 43 (30).

Anal. Calcd for $C_{19}H_{24}O_7$: C, 62.62; H, 6.64; O, 30.76. Found: C, 62.54; H, 6.61; O, 30.47.

Registry No.—1, 38555-39-4.

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Total Synthesis of the Pavinane Alkaloid Platycerine[1]

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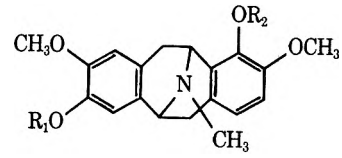
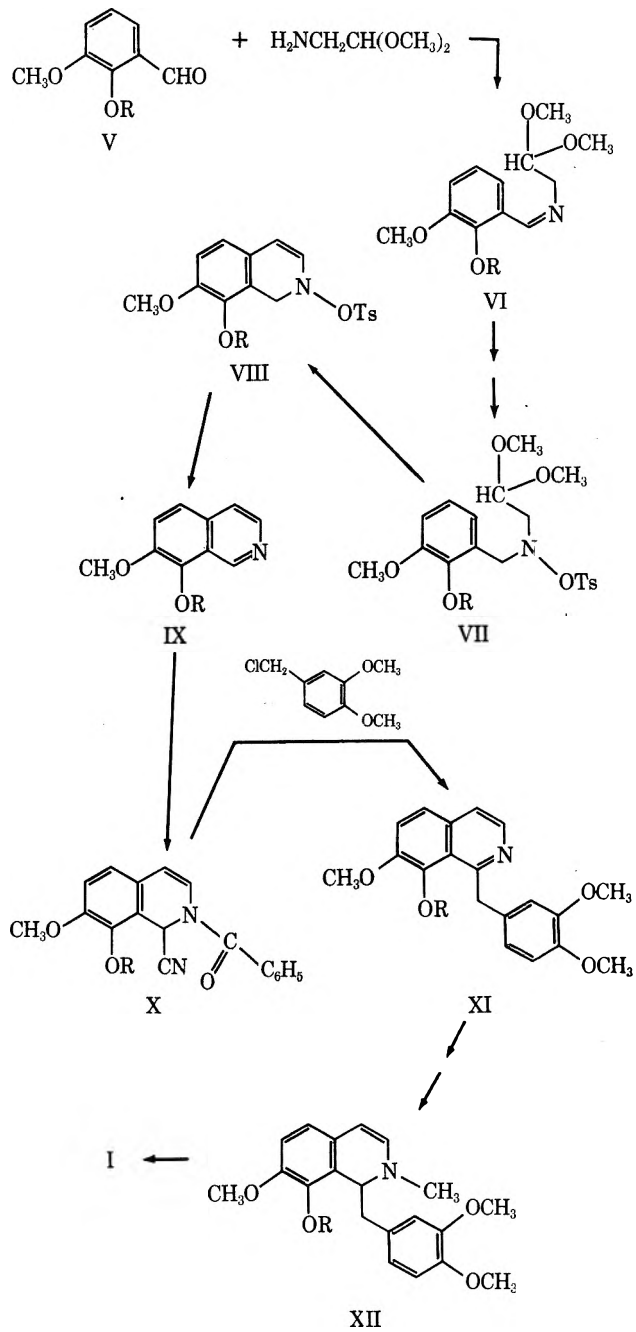
The alkaloid platycerine (I) was first isolated[2] from *Argemone platyceras* Link et Otto. and it was later shown[3] that methylation converted platycerine to *O,O*-dimethylmunitagine (II). II in turn had been prepared[4] by methylation of munitagine (III), whose structure rested[4] upon spectrographic and degradative evidence. Platycerine had also been isolated[5] from *A. gracilenta* Greene and structure I proposed[5] on the basis of its preparation by methylation of munitagine and its mass spectral fragmentation pattern. However, the alternate structure IV for platycerine remained an outside possibility and hence we have synthesized I as final proof of structure.



I, $R_1 = CH_3$; $R_2 = H$
II, $R_1 = R_2 = CH_3$
III, $R_1 = R_2 = H$
IV, $R_1 = H$; $R_2 = CH_3$

Our synthesis was accomplished by means of Scheme I and yielded (±)-platycerine identical with the natural

SCHEME I
(R = $CH_2C_6H_5$)



(1) Part XVI in the series "Alkaloids of the Papaveraceae." For Part XV see F. R. Stermitz, D. K. Kim, and K. A. Larson, *Phytochemistry*, in press. This work was supported in part by NIH Grant GM 19234 from the National Institute of General Medical Sciences and in part by Vipont Chemical Co.

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material (except for optical rotation), and hence structure I for platycerine is confirmed.

Experimental Section

2-Benzyloxy-3-methoxybenzaldehyde (V) was prepared by benzylation of *o*-vanillin according to the method of Uff.[6a] V was obtained in 80% yield as colorless needles (crystallized from ether), mp 44° (lit.[6b] mp 44.0–44.5°).

7-Methoxy-8-benzyloxyisoquinoline (IX).—An adaptation of the method of Jackson and Stewart[7] was used. Intermediates to IX were isolated but were not rigorously purified at each step. A mixture of V and 10% excess aminoacetaldehyde dimethyl acetal was heated in benzene at reflux with a Dean–Stark trap until the calculated amount of water was collected. Excess amino acetal was removed by washing, and distillation *in vacuo* left the product Schiff's base VI as a yellow oil. VI was quantitatively reduced to the amine in ethanol with 1% by weight PtO_2 in a Parr apparatus at 50 psi hydrogen. The amine was converted to the tosylate VII in good yield with *p*-toluenesulfonyl chloride in pyridine. VII (0.1 mol) was dissolved in a solution of 100 ml of peroxide-free dioxane and 15 ml of 6 *M* HCl and the solution was heated at reflux in the dark until tlc showed complete disappearance of VII. The reaction mixture was washed with water and the solvent was removed *in vacuo* to leave VIII as a brown oil. VIII was stirred for several hours in a solution of potassium *tert*-butoxide in *tert*-butyl alcohol under gentle heat. After the mixture had cooled, benzene and water were added and the benzene layer was washed several times with additional water. The benzene layer was dried and the solvent was evaporated to leave a red oil, which was purified by Florisil column chromatography to yield red needles of IX, mp 188° (lit.[6] mp 185–188°), in 60% yield from V.[8]

***N*-Benzoyl-8-benzyloxy-1,2-dihydro-7-methoxyisoquinoline-1-carbonitrile (X).**—To 75 ml (0.15 mol) of an aqueous solution of KCN in an ice-cold three-neck flask fitted with a mechanical stirrer, addition funnel, and condenser was added IX (13 g, 0.05 mol). The mixture was stirred until a fine suspension of IX in the solution was obtained. Benzoyl chloride (0.1 mol) was then added dropwise with stirring. Stirring was continued until the Reissert compound X separated as a tan solid. This was filtered off and recrystallized from ethanol to yield 65% X as a white solid, mp 135° (lit.[6a] mp 135°).

1-(3,4-Dimethoxybenzyl)-7-methoxy-8-benzyloxyisoquinoline (XI).—The nitrile X (12 g in 100 ml of DMF at 0°) was treated under nitrogen with a threefold excess of NaH, and then a twofold excess of 3,4-dimethoxybenzyl chloride in 50 ml of DMF was added. The mixture was stirred overnight and then ethanol was added to destroy the excess NaH. Benzene and water were added and the benzene layer was separated and washed again with water and finally with 6 *M* HCl. The acidic layer was made basic with NaOH and extracted with $CHCl_3$. The $CHCl_3$ layers were combined, dried over K_2CO_3, and evaporated to yield XI in 80% yield. Recrystallization from ethanol gave XI as a white solid: mp 117°; nmr ($CDCl_3$) δ 8.2 (d, 1, H on C_3), 7.7–6.6 (m, 6, aromatic H), 5.0 (s, 2, $OCH_2C_6H_5$), 4.88 (s, 2, CH_2), 3.93 (s, 3, OCH_3), 3.70 (s, 3, OCH_3), 3.60 (s, 3, OCH_3).

Anal. Calcd for $C_{26}H_{25}NO_4$: C, 75.08; H, 5.97; N, 3.29. Found: C, 75.16; H, 6.06; N, 3.37.

(±)-Platycerine (I).—The isoquinoline XI (3 g) was converted to the methiodide by heating in a mixture of 15 ml of CH_3I and CH_3OH. The solvents were removed *in vacuo* and the yellow solid which was obtained was dried and then added to a slurry of $LiAlH_4$ (0.75 g) in dry ether. The slurry was stirred for 3 hr and the excess hydride was decomposed by the addition of wet ether and a saturated solution of sodium potassium tartrate. The ether layer was separated and evaporated to yield the 1,2-dihydroisoquinoline XII as a yellow oil. To XII was added 25 ml of 7:5 $HCOOH$–H_3PO_4 and the solution was heated at reflux until all XII had disappeared as evidenced by tlc. The solution was then diluted with water and washed with $CHCl_3$. The aqueous layer was made basic to pH 8 with NaOH solution and extracted with $CHCl_3$. The $CHCl_3$ layers were combined, dried over K_2CO_3, and evaporated to yield a crude oil shown by tlc and nmr to be the desired I in 60–70% yield. Preparative layer chromatography yielded a sample of pure (±)-platycerine (I) whose $CHCl_3$ ir, $CDCl_3$ nmr, cyclohexane uv, and tlc R_f value (0.55 using silica gel G and 3:2 benzene–methanol) were identical with those of the natural alkaloid.[4]

Registry No.—I, 38863-79-5; V, 2011-06-5; VI, 38868-50-7; VII, 38868-51-8; VIII, 38868-52-9; IX, 36454-41-8; X, 38868-54-1; XI, 38868-55-2.

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(8) We are indebted to Mr. John Lawson for technical assistance in this preparation.

The Photocycloaddition of Diphenylacetylene to 1,5-Cyclooctadiene

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It is known that diphenylacetylene photoreacts with tetramethylethylene[1] and cyclic vinyl ethers[2] to give the cyclobutene derivatives. In an earlier paper[3] we reported the photocycloaddition of diphenylacetylene to norbornadiene, in which the products that were considered to be formed by the further reactions of the intermediate cyclobutene were obtained in contrast to the above reactions. In order to observe the behavior of diphenylacetylene in other dienes, we photolyzed a solution of diphenylacetylene in 1,5-cyclooctadiene. The reaction mixture was irradiated for 40 hr through a Pyrex filter with a high-pressure mercury lamp. Chromatography on silica gel gave only one product, **1** (72%).

Elemental analysis and the mass spectrum (M^+ 286) indicated that this product was a 1:1 adduct of diphenylacetylene and 1,5-cyclooctadiene. The nmr spectrum showed no signals in the vinyl region, and was very simple, indicating that this product has the symmetrical structure. The possible structure for this product is **1** or **2**, whose type of structure was assigned to the photoadduct of acetylenedicarboxylic acid and 1,4-cyclohexadiene.[4,5]

This product was stable on heating for 1 hr at 47° in 2 *N* sulfuric acid, where norcarane completely decomposed,[6] and the signal at δ 3.04 is at too low field to be assigned to the ring protons of cyclopropanes.[7] Structure **1** is compatible with these properties, but structure **2** is not. Thus, this product was assigned the structure 9,10-diphenyltetracyclo[6.2.0.$0^{4,10}$.$0^{5,9}$]-decane.

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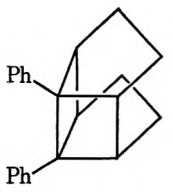
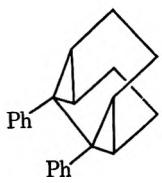


1



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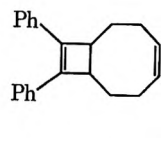

3

This reaction was neither sensitized by thioxanthone (E_T = 65.5 kcal/mol)[8] and triphenylene (E_T = 66.6 kcal/mol),[8] whose triplet energies are considered to be effectively transferred to diphenylacetylene (E_T = 62.5 kcal/mol),[8] nor quenched by diacetyl (E_T = 54.9 kcal/mol).[8] These results suggest that the addition involves singlet-excited diphenylacetylene; this is a contrast to the results that other photoreactions of diphenylacetylene proceeded *via* triplet diphenylacetylene.[2,9] This reaction is considered to involve the intramolecular photocycloaddition of the intermediate cyclobutene **3**. However, this intermediate was never observed when the photolysis was monitored by glc and uv. This can be well explained by the assumptions that the intermediate diphenylcyclobutene **3** is preferentially photoexcited on account of its large molar extinction coefficient[10] at the excitation wavelengths, and the quantum efficiency of the intramolecular reaction is greater than that of diphenylacetylene with 1,5-cyclooctadiene.

Experimental Section

Melting points are uncorrected. Ir spectra were obtained on a Hitachi EPI-S2 spectrophotometer. Uv spectra were obtained on a Hitachi 124 spectrophotometer. Mass spectra were obtained on a Hitachi RMS-4 spectrometer. Nmr spectra were taken on a high Hitachi Perkin-Elmer R-20 spectrophotometer. Glc was performed on a Simadzu GC-3AF (2 m × 3 mm, 3% SE-30 on Chromosorb W column).

Photoaddition of Diphenylacetylene and 1,5-Cyclooctadiene.—In a Pyrex vessel, a solution of diphenylacetylene (0.8 g, 0.0045 mol) in 1,5-cyclooctadiene (48 g, 0.44 mol) was irradiated for 40 hr with a 350-W high-pressure mercury lamp. After removal of the unreacted diene under reduced pressure, the remaining liquid (1.4 g) was subjected to column chromatography on Merck silica gel, 50 g (70–230 mesh). Elution in 200-ml fractions gave fractions 1–3, *n*-hexane, nil; 4–5, 5% benzene in *n*-hexane, a crystalline material. Recrystallization of this crystalline material from ethanol gave 9,10-diphenyltetracyclo[6.2.0.0^{4,10}.0^{5,9}]-decane: 924 mg (72%); mp 105.5–106.5°; ir (KBr) 3040, 3010, 2930, 1595, 1487, 1440, 750, 721, and 695 cm^{-1}; nmr (CCl_4) δ 2.0 (m, 8 H, methylene), 3.04 (br s, 4 H, cyclobutane), and 7.0 (m, 10 H, aromatic); mass spectrum *m/e* (rel intensity) 286 (1), 144 (48), 143 (100), 142 (83), 128 (39), 115 (15), and 91 (11); uv (*n*-hexane) 223 nm (ϵ 10,700), 248 (1500), 253 (920), 262 (800), and 272 (490).

Anal. Calcd for $C_{22}H_{22}$: C, 92.26; H, 7.74. Found: C, 92.25; H, 7.56.

Attempted Sensitization with Thioxanthone and Triphenylene.—Diphenylacetylene (50 mg, 0.28 mmol), 1,5-cyclooctadiene (300 mg, 2.78 mmol), and thioxanthone (10 mg, 0.047 mmol) or triphenylene (10 mg, 0.044 mmol) in benzene (3 ml) were irradiated through a liquid filter (an aqueous solution of NaBr and $Pb(NO_3)_2$, >330 nm)[11] with the 350-W high-pressure mercury lamp for 20 hr. However, the product was not observed by glc.

Attempted Quenching with Diacetyl.—Each of two quartz tubes was charged with 3 ml of a solution of diphenylacetylene (0.0337 *M*) and 1,5-cyclooctadiene (0.926 *M*) in cyclohexane. Diacetyl (44 mg, 0.512 mmol) was added to one of the tubes. The tubes were irradiated for 2 hr at 254 nm in which most of the light was absorbed by diphenylacetylene. No quenching was observed by glc.

Registry No.—**1**, 38821-22-6; diphenylacetylene, 501-65-5; 1,5-cyclooctadiene, 111-78-4.

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Sterol Metabolism. XXIII. Cholesterol Oxidation by Radiation-Induced Processes[1]

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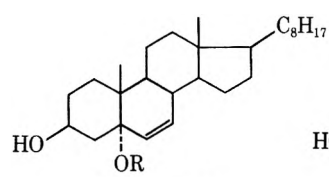
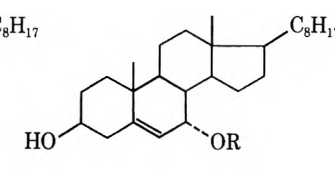
Received December 20, 1972

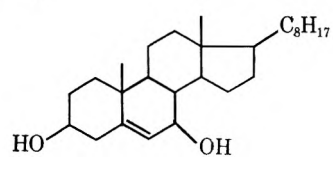
The common cholesterol oxidation products 3β-hydroxycholest-5-en-7-one (IV), cholesta-3,5-dien-7-one (V), and the epimeric cholest-5-ene-3β,7-diols (IIb, IIIb) derive by thermal decomposition of sterol hydroperoxides formed by two distinct mechanisms from cholesterol. Photosensitized oxidation of cholesterol in solution by excited-state (singlet) molecular oxygen gives 3β-hydroxy-5α-cholest-6-ene-5-hydroperoxide (Ia),[3] which may rearrange in solution to the 7α-hydroperoxide IIa,[3c,4] which in turn may epimerize to the 7β-hydroperoxide IIIa.[5] Alternatively,



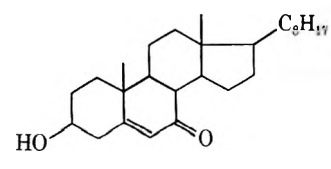
Ia, R = OH
b, R = H



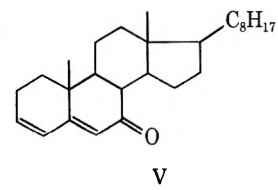
IIa, R = OH
b, R = H



IIIa, R = OH
b, R = H



IV



V

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(2) Robert A. Welch Foundation Postdoctoral Fellow, 1971–1972.

(3) (a) G. O. Schenck, *Angew. Chem.*, **69**, 579 (1957); (b) G. O. Schenck, K. Gollnick, and O.-A. Neumüller, *Justus Liebigs Ann. Chem.*, **603**, 46 (1957); (c) G. O. Schenck, O.-A. Neumüller, and W. Eisfeld, *ibid.*, **618**, 202 (1958); *Angew Chem.*, **70**, 595 (1958); (d) A. Nickon and J. F. Bagli, *J. Amer. Chem. Soc.*, **81**, 6330 (1959); **83**, 1498 (1961).

(4) B. Lythgoe and S. Trippett, *J. Chem. Soc.*, 471 (1959).

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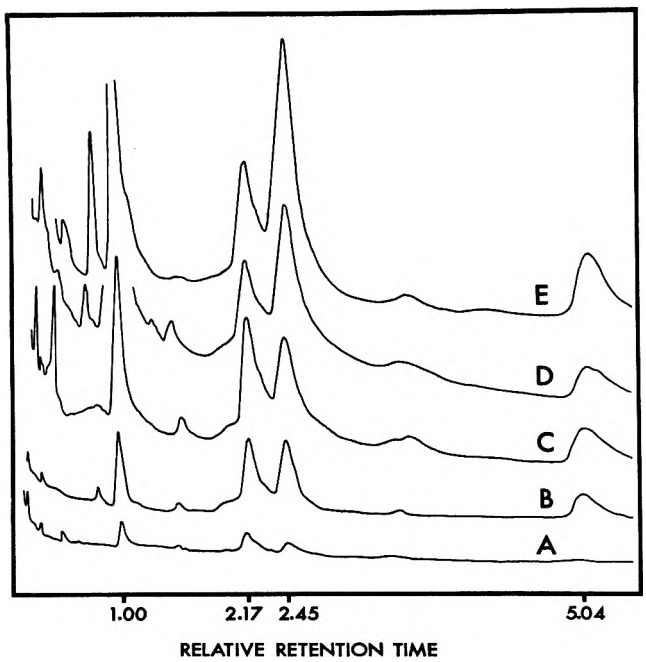

Figure 1.—Gas chromatographic (3% OV-210) detection of IIIa *via* its pyrolysis products IIIb, IV, and V (at retention times relative to cholesterol as unity of 2.45, 5.04, and 2.17 respectively): A, control; B, ^{60}Co γ radiation, 7×10^4 rad; C, 254-nm light, 1 hr; D, daylight, 6 days; E, 100° heat, 42 hr.

radical oxidation of cholesterol in solution may afford cholesterol 7-peroxy radicals or 7-hydroperoxides.[6-8] In either case the initially formed hydroperoxides give rise to the more common secondary products IIb, IIIb, IV, and V (but not Ib).

Radiation-induced oxidation of crystalline cholesterol leads to the same secondary products IIb, IIIb, IV, and V,[9] but the mechanism of their formation in the solid state has not heretofore been examined. By means of suitable chromatographic techniques[1,9d,10] (see Figure 1) we demonstrated that the initial and major sterol hydroperoxide formed from crystalline cholesterol subjected to a variety of irradiation conditions was the 7β-hydroperoxide IIIa, with small amounts of the 7α-hydroperoxide IIa formed later in the reactions. Radiations ranging from ^{60}Co γ rays through ultraviolet and visible light to infrared heat all afforded IIIa as that hydroperoxide first detected. No 5α-hydroperoxide Ia was detected. Under radiation conditions producing IIIa from cholesterol, the 5α-hydroperoxide Ia was not rearranged to the 7α-hydroperoxide IIa, nor was IIa epimerized. However, Ia, IIa, and IIIa were partially decomposed to their thermal decomposition products IIb, IIIb, IV, and V on longer exposure to radiation.

These results eliminate formation of the 5α-hydroperoxide Ia as a pathway (*via* IIa) to IIIa and accordingly participation of singlet molecular oxygen by the established cyclic ene mechanism. Furthermore, we did not detect the 7β-hydroperoxide IIIa in photosensitized oxidations of cholesterol despite a careful chromatographic examination. We thereby confirm prior findings on this point derived by less certain means.[3d] We conclude that IIIa is not a product of singlet molecular oxygen attack on cholesterol in solution or in the solid state.

Formation of IIIa from cholesterol was independent of the type of radiation used, and we consider that radical processes are implicated.[11] Initial generation of a C-7 allylic radical followed by reaction with ground-state (triplet) molecular oxygen to form a cholesterol 7-peroxy radical is supported by published electron spin resonance data.[13] Subsequent C-7 hydrogen atom abstraction by the 7-peroxy radical from another cholesterol molecule would then afford the product 7-hydroperoxides IIIa and IIa and continue the radical chain. Preferential formation of the quasiequatorial 7β-hydroperoxide IIIa in a radial process may be rationalized by consideration of the demonstrated greater thermodynamic stability of IIIa.[5] Formation of smaller amounts of IIa is thereby a random or statistically fortuitous matter. However, some preference in radical generation and attack of molecular oxygen may obtain from the crystal properties of cholesterol, for we have previously demonstrated that autoxidation of crystalline cholesterol yields 24-hydroperoxides in approximately 2:1 ratio rather than in the expected 1:1 ratio.[12a]

Autoxidation of cholesterol dispersed in aqueous sodium sterarate solutions[8a,b] similarly afforded only the 7-hydroperoxides IIa and IIIa as initially formed products, with no 5α-hydroperoxide Ia detected. Radical autoxidation of cholesterol accordingly may occur in solution, in the dispersed state, and in the solid state. The sensitive chromatographic methods used in these studies suggest anew the great ease with which highly purified cholesterol is oxidized in air. The unirradiated control (curve A of Figure 1) obtained by mere recrystallization of a highly purified cholesterol sample clearly contained the 7β-hydroperoxide IIIa, as evinced by the presence of the pyrolysis products IIIb and V on the elution curve.[14]

Access to the 7β-hydroperoxide IIIa has heretofore been *via* epimerization of IIa, in which case tedious

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(10) L. L. Smith and F. L. Hill, *J. Chromatogr.*, **66**, 101 (1972).

(11) We have previously suggested radical pathways involving ground-state (triplet) molecular oxygen as means of formation of the cholesterol 20α-, 24-, 25-, and 26-hydroperoxides from cholesterol.[9e,12]

(12) (a) J. E. van Lier and L. L. Smith, *J. Org. Chem.*, **36**, 1007 (1971); (b) J. E. van Lier and G. Kan, *ibid.*, **37**, 145 (1972).

(13) (a) W. Gordy, *Radiat. Res., Suppl. 1*, 491 (1959); (b) H. N. Rexrod and W. Gordy, *Proc. Nat. Acad. Sci. U. S.*, **45**, 256 (1959); (c) A. Ehrenberg, L. Ehrenberg, and G. Loforth, Danish Atomic Energy Commission Research Establishment, Risö, Report No. 16, 1960, cited in B. H. J. Bielski and J. M. Gebicki, "Atlas of Electron Spin Resonance Spectra," Academic Press, New York/London, 1967, pp 146–147; (d) O. Hellinger, *Biophysik*, **6**, 63 (1969).

(14) The exceptional stability of a sample of cholesterol (purified *via* the dibromide) after 34 years of storage in contact with air [*cf.* L. L. Engel and P. Brooks, *Steroids*, **17**, 531 (1971)] remains unexplained. Our chromatographic examination of the sample kindly supplied by Professor Engel failed to demonstrate the presence of any sterol hydroperoxides or secondary autoxidation products.

separation of IIIa from thermal decomposition products and from IIa was necessary. Accordingly, radiation-induced oxidation of cholesterol is of some preparative utility. Yields of 5.8–7.4% of 1,2-^{3}H-IIIa free from other detectable sterols have been attained from 1,2-^{3}H-cholesterol by irradiation with ^{60}Co γ radiation for 8 hr.

Experimental Section[15]

Radiation Conditions.—Samples (2 and 5 g) in glass beakers of crystalline cholesterol (purified to a high degree by multiple recrystallizations from methanol and in which no autoxidation component could be detected) were exposed in air to four radiation conditions. Samples were exposed to ^{60}Co γ rays in a Gammacell 200 (Atomic Energy of Canada Ltd., Ottawa) providing 2.7×10^5 rad/hr. After 15 min the 7β-hydroperoxide IIIa was readily detected. Other samples were exposed to a 254-nm germicidal ultraviolet light for 1 hr at a distance of 10 cm, after which time IIIa was readily detected. Samples were exposed to daylight and air on the laboratory bench for 6 days, at which time IIIa was readily detected. Samples were heated at 100° in an electric oven. After 42 hr IIIa was readily detected.

Sample Preparation.—Irradiated samples were dissolved (2 g/40 ml, 5 g/100 ml) in the dark at 40° under N_2 in diethyl ether–methanol (1:1). Chilling to 5° yielded crystalline cholesterol which was filtered off for analysis. The mother liquor was concentrated under vacuum to incipient crystallization, and a second crop of crystalline cholesterol was removed. Concentration under vacuum was repeated until the mother liquor volume was 5 ml (for 2-g samples) or 10 ml (for 5-g samples). The concentrated mother liquor was preparatively chromatographed on 0.25 mm chromatoplates of silica gel HF_{254} using benzene–ethyl acetate (17:8) in triple ascending irrigations. The sterol hydroperoxide zone was located and eluted from the chromatoplate with 5–10 ml of acetone, the acetone was removed under vacuum, and the sterol residue was redissolved in 100 μl of acetone for analysis.

Replicate experiments were handled by a more direct method. The mother liquor obtained by crystallization of cholesterol and concentration was evaporated under vacuum and the sterol residue was subjected to analysis without intermediate preparative thin layer chromatography. Essentially identical results were obtained by the two different sample preparation methods.

Sample Analysis.—Mother liquor sterols in 100 μl of acetone were subjected to thin layer chromatography with up to 100–200 μg of total sterols applied to the chromatoplate per analysis. Reference sterols were run on the same chromatoplate. Each sample was analyzed as such and also after reduction on the chromatoplate with 20 μl of a 10% sodium borohydride solution in methanol.[17] In that no 7-ketone IV was detected in these samples by ultraviolet light absorption of the chromatoplate reduction with borohydride gave product alcohols solely from the sterol hydroperoxides present. Each chromatoplate was visualized with *N*,*N*-dimethyl-*p*-phenylenediamine and 50% sulfuric acid for identification with confidence of each detected sterol component. In each case IIIa was the first sterol product to be detected in irradiated samples, with IIa forming more slowly and at much reduced levels. No Ia could be detected as such or as the reduced product Ib.

Samples of mother liquor (2–10 μl) were analyzed by gas chromatography on SP-2401 and OV-210 columns at the same time.[1] Uniform and characteristic elution curves were obtained for all samples, in which IIIa and V predominated. Typical elution curves are given in Figure 1 in which 3% OV-210 columns were used. Key relative retention times noted are 1.00, reference cholesterol; 2.17, VI; 2.45, IIIb; 5.04, IV. Cholesta-4,6-dien-3-one would appear at 3.46 and IIIb at 2.27.

Stability Experiments.—Pure samples of Ia, IIa, and IIIa were exposed to the same irradiation conditions. In the case of ^{60}Co γ radiation, exposure times of 30 min were also used. Analysis of these samples by both thin layer and gas chromatography established that thermal decomposition only had occurred, with no evidence of conversion of Ia to IIa, of IIa to IIIa, or of conversion of IIIa to other hydroperoxides.

1,2-^{3}H-Cholesterol 7β-Hydroperoxide (IIIa).—An aliquot (*ca.* 10 μCi) of 1,2-^{3}H-cholesterol was chromatographed on 0.25 mm thick silica gel HF_{254} chromatoplates irrigated three times with benzene–ethyl acetate (17:8), and the eluted radioactive cholesterol was rechromatographed a second time. Dilution with 500 mg of crystalline highly purified carrier cholesterol gave a sample assaying 29,700 dpm/mg. A portion of this material (200 mg) in a small glass vial open to the air was irradiated with ^{60}CO γ radiation for 8 hr, after which time the irradiated sample was dissolved in 200 ml of methanol, chilled overnight, and the resultant crystalline 1,2-^{3}H-cholesterol filtered. The solvent was evaporated under vacuum, and the sterol residue was dissolved in a minimum volume of acetone and chromatographed on 0 25 mm thick silica gel HF_{254} chromatoplates using benzene–ethyl acetate (17:8) with triple irrigation in the usual fashion. The IIIa zone was located and excised from the chromatoplate. The 1,2-^{3}H-IIIa was eluted with acetone. Rechromatography of the material twice more using the same system sufficed to give pure 1,2-^{3}H-IIIa free from IIa and other detectable sterols. Only one component (1,2-^{3}H-IIIa) was detected on thin layer chromatograms or on gas chromatography on 2% SP-2401. Sodium borohydride reduction gave only one radioactive component identified as IIIb, with no other detectable sterols present. The radioactive IIIa was dissolved in 1 ml of acetone, and 50-μl aliquots were assayed for radioactivity to determine yields of 5.8 and 7.4% for two separate preparations.

Registry No.—Cholesterol, 57-88-5.

(15) Solvents were redistilled prior to use. All sterols used were of high purity as judged by melting point, infrared absorption spectral, and thin layer and gas chromatographic criteria. Thin layer chromatography was conducted on 0.25 mm thick 20 × 20 cm chromatoplates of silica gel HF_{254} (E. Merck GmbH., Darmstadt) using benzene–ethyl acetate (17:8) and triple ascending irrigation by techniques previously described in detail.[9d] Typical mobility data with IIIa serving as unit mobility follow: IIIa, 1.00; IIa, 0.91; Ia, 0.91; IIb, 0.53; IIIb, 0.60; Ib, 0.76. Sterol hydroperoxides were detected by *N*,*N*-dimethyl-*p*-phenylenediamine used as a spray.[10] Sterols were also detected by their characteristic colors developed with 50% aqueous sulfuric acid used as a spray.[9d]

Gas chromatography was conducted by procedures previously described in detail,[16] but using 2–3% SP-2401 and 2–3% OV-210 liquid phases on 100–120 mesh Supelcoport (Supelco Inc., Bellefonte, Pa.) for the confident resolution of IIb and IIIb.[1] Retention data for the several sterols involved in this study were essentially the same as those previously reported.[1]

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The Stereoselectivities of Lithium Aluminum Trialkoxyhydrides

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The modification of lithium aluminum hydride ($LiAlH_4$) by the addition of various alcohols (or ketones), and subsequent use of the resulting lithium aluminum alkoxyhydrides (1) in the reduction of the model system dihydroisophorone (2), has led to two basic conclusions.[1] First, lithium aluminum alkoxyhydrides are generally more highly stereoselective than $LiAlH_4$ itself, presumably because of the greater bulk of the alkoxyhydride reagents. It was recognized[1,2] that certain alkoxyhydrides, such as lithium aluminum tri-*tert*-butoxyhydride, were less stereoselective than their apparent bulk suggested. This was explained by Ashby and coworkers,[3] who showed that, while the

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(2) H. C. Brown and H. R. Deck, *ibid.*, **87**, 5620 (1965); for a review on alkoxyaluminum hydrides, see J. Malek and M. Cerny, *Synthesis*, (5), 217 (1972).

(3) E. C. Ashby, J. P. Sevenair, and F. R. Dobbs, *J. Org. Chem.*, **36**, 197 (1971).

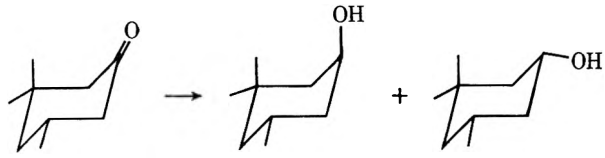
reagents 1 may be associated in tetrahydrofuran, lithium aluminum tri-*tert*-butoxyhydride was monomeric over a wide concentration range. Furthermore, association was shown to be an important factor in determining stereoselectivity.

The second conclusion was that the reductions of certain ketones with $LiAlH_4$ do not appear to involve the intervention of lithium aluminum alkoxyhydrides (1) as active reducing species owing to a proposed rapid disproportionation of such species to $LiAlH_4$, the only effective reducing agent, and to $LiAl(OR)_4$,[1] for example, eq 1.

$$\underset{\mathbf{1}}{4LiAlH(OR)_3} \longrightarrow 3LiAl(OR)_4 + LiAlH_4 \qquad (1)$$

The main evidence for the above proposal involves the following: (1) an insensitivity of stereoselectivity to method of reduction, *i.e.*, direct addition using excess hydride or inverse addition of an equivalent quantity of hydride;[1,4,5] (2) instability of **1** when R is isopropyl or *sec*-butyl;[6] (3) AlH_4^- is more reactive than $LiAlH(OR)_3$;[6,7] (4) the intermediate species **1** presumably formed by reaction of $LiAlH_4$ with 3 mol of addend isopropyl alcohol or cyclohexanone showed the same stereoselectivity in the reduction of dihydroisophorone (2) as $LiAlH_4$ itself.[1,8,9]

This paper reports studies of the stereoselectivities of alkoxyhydrides (1) formed from the reaction of 3 mol of primary or secondary alcohols (or ketone) with $LiAlH_4$, using dihydroisophorone (2) as the model



2 *trans*-3 *cis*-3

ketone substrate. It extends the scope of the earlier work,[1] describes a new, highly stereoselective reagent, and discusses the effect of the steric requirements of the reagent as a factor in stereoselective reductions. The results are shown in Table I, which also includes some earlier data[1] for comparison.

Results

Entry 1, Table I, shows the reduction of 2 with $LiAlH_4$ itself, entries 2–5 show the effects on stereoselectivity of a series of primary alkoxy groups of increasing steric size, while entries 6–10 do the same for secondary alkoxy groups.

Considering the primary alkoxyhydrides, it is seen from Table I that the reagents formed from methyl alcohol and ethyl alcohol (entries 2 and 3) show greater stereoselectivity than $LiAlH_4$ itself. The more highly hindered isobutyl alcohol (entry 4) and neopentyl alcohol (entry 5), however, form *less* stereoselective reagents. The reason is probably that given by Ashby,[3] that the methoxyhydride (and probably also ethoxyhydride) reagents are highly associated. This would imply that the isobutoxyhydride and neopentoxyhydride are less associated and possibly monomeric. This is consistent with the greater bulk of these latter two reagents, which may reduce association effects. The highly hindered lithium aluminum tri-*tert*-butoxyhydride was found to be monomeric in THF.[3]

TABLE I

REDUCTION OF 2 WITH $LiAlH_4$ AND MODIFIED REAGENTS[a]

Entry	Addend[b]	Reagent concn[c]	*trans*-(axial) **3**, %
1		0.76	52–55,[d,e] 53[f]
2	CH_3OH		75[d]
3	CH_3CH_2OH		83[d]
4	$(CH_3)_2CHCH_2OH$	0.31	57[f,g]
5	$(CH_3)_3CCH_2OH$	0.19, 0.48	60,[f,h] 60[f,i,j]
6	$CH_3CHOHCH_3$	0.40	54,[d] 55[f,k]
7	$CH_3CH_2CHOHCH_3$	0.19	63[f,l]
8	$(CH_3)_2CHCHOHCH_3$	0.19	59[f,m]
9	$(CH_3)_3CCHOHCH_3$	0.31, 0.19, 0.06	75,[f] 77,[f,n] 80[f,o]
10	$(CH_3)_3CCOC(CH_3)_3$	0.48	98[f,p]
11	Cyclohexanone		58[d,q]
12	Cyclopentanol	0.31	57[f,r]

[a] In diethyl ether. [b] 3 mol addend per mole ketone. [c] Molarity after addition of addend to $LiAlH_4$. [d] Reference 1. [e] Includes direct and inverse method of addition. [f] This work. [g] *Ca.* 1% **2** in product. [h] 34% **2** in product. [i] Separate experiment. [j] 10% **2** in product. [k] Trace of **2** in product. [l] 48% **2** in product. [m] 16% **2** in product. [n] 9% **2** in product. [o] 31% **2** in product. [p] 6% **2** in product. [q] 48% **2** in product. [r] 13% **2** in product.

The data for the secondary alkoxyhydrides are quite interesting. Reagents formed from isopropyl alcohol, *sec*-butyl alcohol, 3-methyl-2-butanol, cyclohexanone, and cyclopentanol (entries 6–8, 11, 12) showed the same or slightly higher stereoselectivities as $LiAlH_4$. This could either mean that the disproportionation mechanism[1] of hydride reduction is correct or it could be that *these* alkoxyhydrides are simply not stereoselective in the reduction of 2. However, the reagents formed from 3,3-dimethyl-2-butanol (entry 9) and di-*tert*-butyl ketone (entry 10) are highly selective, with the latter giving the less stable axial alcohol[10] almost exclusively. Clearly, with these two more hindered secondary addends, disproportionation cannot be a major factor. It may be that steric hindrance (B strain) lowers the stability of the disproportionation product, *i.e.*, the tetraalkoxyaluminum species.[11] While experiments establishing the degree of association of these reagents would be useful,[3] it does not appear likely that the increase in stereoselectivity in going from entry 8 to entry 9 and then to entry 10 can be due to a significant increase in association, and the increase is attributed to steric approach control[8] due to the bulky alkoxy groups. It should be noted that lithium aluminum tri-*tert*-butoxyhydride is quite highly selective in the reduction of 2 in both ether (73% *trans*-**3**) and tetrahydrofuran (88% *trans*-**3**).[1]

While considerable amounts of unreacted 2 were found in some of the reduction products (Table I), equilibration of the products is known not to occur in these hydride reductions.[9,12,13] Duplicate experiments showed that the results are highly reproducible.

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(13) O. R. Vail and D. M. S. Wheeler, *J. Org. Chem.*, **27**, 3803 (1962).

In summary, the steric bulk of primary alkoxy groups in alkoxyhydrides (1) does not appear to have a major effect on their stereoselectivities. However, bulky secondary (and tertiary) alkoxy groups provide reagents with considerable steric requirements. The reagent formed from di-*tert*-butyl ketone is a remarkably highly selective one and should prove useful in synthetic applications. The great preference for formation of the less stable isomer, *trans*-**3**, compares with that observed in the kinetically controlled reduction of **2** with triisobutylaluminum.[14]

Experimental Section

Isopropyl alcohol, *sec*-butyl alcohol, isobutyl alcohol, and cyclopentanol were chromatoquality reagents purchased from Matheson Coleman and Bell. The other addends were commercially obtained and their purities were checked by glc. Gas–liquid partition chromatography was carried out with a Hewlett-Packard 5750 gas chromatograph. For the analyses of the reduction product, a 10-ft 10% Carbowax 20M acid washed and silanized column was used at 145°.

Reaction of $LiAlH_4$ with 3,3-Dimethyl-2-butanol. Reduction of Dihydroisophorone (2).—The procedure for this reaction is typical of that used in all the reductions. Standardized lithium aluminum hydride in ether (40 ml, 0.28 *M*, 0.011 mol of $LiAlH_4$) was added by pipet to a 250-ml reactor equipped with a magnetic stirrer, equilibrated addition funnel, and condenser. A solution of the alcohol (3.373 g, 0.033 mol) in 15 ml of diethyl ether was added dropwise, with stirring. After stirring for 20 min, a solution of **2**[10] (1.54 g, 0.011 mol) in 10 ml of ether was added dropwise. After 30 min, the cooled reaction mixture was hydrolyzed with water, followed by 10% sulfuric acid. The aqueous portion was extracted with ether and the combined ether solution was washed with saturated sodium bicarbonate and salt solution and dried over anhydrous $MgSO_4$. The solution was concentrated by distillation through a 18-in. helix packed fractionating column (oil bath temperature to 63°). The concentrated solution was directly analyzed by glc showing 77% of the *trans* (axial)-**3** and 23% of *cis*-**3**. Unreacted **2** represented 9% of the three components.

Registry No.—**1** (R = H), 16853-85-3; **1** (R = Me), 12076-93-6; **1** (R = Et), 17250-30-5; **1** (R = *i*-Bu), 38884-26-3; **1** [R = $(CH_3)_3CCH_2$], 38884-27-4; **1** (R = *i*-Pr), 38960-86-0; **1** (R = *sec*-Bu), 38884-28-5; **1** [R = $(CH_3)_2CHCHCH_3$], 38884-29-6; **1** [R = $(CH_3)_3$-$CCHCH_3$], 38884-30-9; **1** (R = *t*-BuCHBu-*t*), 38884-31-0; **1** (R = cyclohexyl), 38884-32-1; **1** (R = cyclopentyl), 38884-33-2; **2**, 873-94-9; *cis*-**3**, 933-48-2; *trans*-**3**, 767-54-4; 3,3-dimethyl-2-butanol, 464-07-3.

(14) H. Haubenstock and E. B. Davidson, *J. Org. Chem.*, **28**, 2772 (1963).

Base-Induced Cyclizations of Diethyl 4-Oxa-6-heptyne-1,1-dicarboxylate[1]

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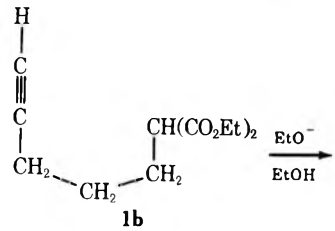
As a continuation of efforts[2] directed toward determining the scope and limitations of reactions with base of compounds that can be represented generally by **1**, we prepared diethyl 4-oxa-6-heptyne-1,1-di-

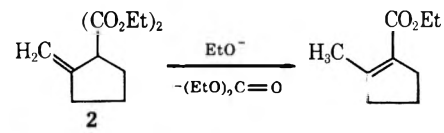
$$HC{\equiv}CCH_2Y(CH_2)_nZH$$
1

carboxylate [**1a**, Y = O, Z = $C(CO_2Et)_2$, n = 2] and studied its reaction with sodium ethoxide in ethanol and potassium *tert*-butoxide in dimethyl sulfoxide.

Eglinton and Whiting[3] reported that it was possible to isolate 1,1-dicarboethoxy-2-methylenecyclopentane (**2**) from the reaction of diethyl malonate, sodium ethoxide, and 4-pentynyl *p*-toluenesulfonate in refluxing ethanol, and they showed that the product arose by cyclization of the intermediate diethyl 5-hexyne-1,1-dicarboxylate [**1b**, Y = CH_2, Z = $C(CO_2Et)_2$, n = 1].[4] They ob-



1b



2

served that, when more than 1 equiv of sodium ethoxide was used, decarboethoxylation of the cyclic diester and migration of the double bond took place.

Significantly, Eglinton and Whiting[3] found that diethyl 6-heptyne-1,1-dicarboxylate [**1**, Y = CH_2, Z = $C(CO_2Et)_2$, n = 2] would not cyclize under conditions which converted **1b** to **2**.

1a was prepared conveniently by alkylation of diethyl malonate with 6-bromo-4-oxa-1-hexyne.[5] Treatment of **1a** with a slight excess of sodium ethoxide in boiling ethanol for 8 hr gave a 78% conversion to a 1:1.4 mixture of 4-carboethoxy-5,6-dihydro-3-methyl-1,4-oxin (**3**) and 4-carboethoxy-2,3,6,7-tetrahydrooxepin (**4**), which could be separated by fractional distillation. In a separate experiment a 74% yield of diethyl carbonate was also obtained. Structures were assigned to **3** and **4** on the basis of their spectroscopic properties and analytical data.

By analogy with the behavior of propargyloxyethanols (**1**, Y = Z = O, n = 2) when treated with base in hydroxylic solvents,[2a] the first step in formation of **3** and **4** can be pictured as intramolecular nucleophilic addition of substituted malonate anion to the internal and terminal acetylenic carbons to give the diesters **3a** and **4a**.[6] In the presence of excess base, this is followed by decarboethoxylation of the diesters with formation of diethyl carbonate and migration of the double bonds. It seems likely that decarboethoxylation

(1) Supported in part by Grant CA-10740 from the U. S. Public Health Service.

(2) (a) A. T. Bottini and J. G. Maroski, *J. Org. Chem.*, **38**, 1455 (1973); (b) A. T. Bottini and E. F. Böttner, *ibid.*, **31**, 586 (1966), and references cited therein.

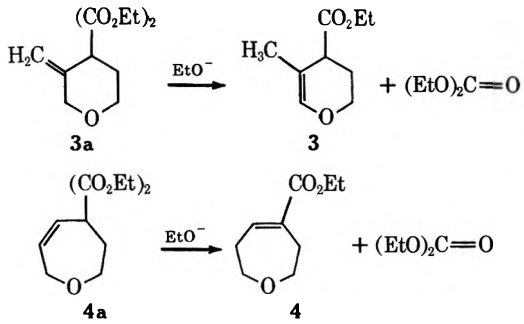
(3) G. Eglinton and M. C. Whiting, *J. Chem. Soc.*, 3052 (1953).

(4) Similar cyclizations of *cis*-hex-5-yn-3-ene-1,1-dicarboxylates to 1,1-dicarboethoxy-2-methylene-3-cyclopentenes have been reported. See M. V. Mavrov and V. F. Kucherov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1559 (1967), and references cited therein.

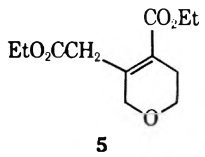
(5) D. Black, S. Landor, A. Patel, and P. Whiter, *J. Chem. Soc. C*, 2260 (1967).

(6) The faster rate of cyclization of **1a** relative to diethyl 6-heptyne-1,1-dicarboxylate[3] on treatment with sodium ethoxide in ethanol is most likely due to the electron-withdrawing effect of oxygen, which makes the acetylenic carbons more susceptible to nucleophilic attack.

of **3a** first gives the α,β-unsaturated ester, which is then converted to more stable **3**.



The reaction of **1a** with potassium *tert*-butoxide in dimethyl sulfoxide was also investigated. This reaction gave a relatively poor yield (<20%) of a complex mixture of six cyclic products, and the major products were identified as **3**, 4-carboethoxy-5,6-dihydro-3-ethoxycarbonylmethyl-1,2-oxin (**5**), and the *tert*-butyl homolog

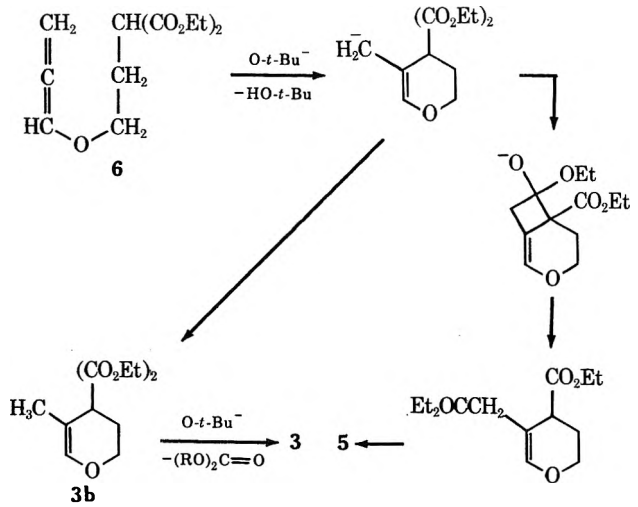


5

of **3**. The last product was identified solely on the basis of its nmr spectrum.

The absence of the seven-membered ring product **4** from the product mixture indicated that **3** may have been formed in dimethyl sulfoxide by a pathway that did not involve direct cyclization of **1a**. Again by analogy with the behavior of propargyloxyethanols under comparable reaction conditions,[2a] an alternative mechanism leading to **3** can be pictured. In this mechanism, **1a** first undergoes prototropic rearrangement to give diethyl 4-oxa-5,6-heptadiene-1,1-dicarboxylate (**6**), which cyclizes by intramolecular nucleophilic addition of malonate to the central allene carbon to give the diester **3b**; decarboethoxylation of **3b** then gives **3**.

Intermediacy of the allene **6** also yprovides a reasonable explanation for the novel trans carboethoxylation leading to **5**. In addition to undergoing protonation to give **3b**, the cyclic carbanionic intermediate can also



give **5** *via* a bicyclic intermediate formed by addition of the carbanion to carbonyl carbon.

In addition to **1a**, several related compounds (**1**, Y = O, Z = $CHCO_2H$, n = 2; **1**, Y = O, Z = $CHCO-CH_3$, n = 2; **1**, Y = O, Z = CO_2^-, n = 2) were prepared and their reactions with base were investigated. None of the reactions gave a cyclic product formed by intramolecular nucleophilic addition to unsaturated carbon.[7]

Experimental Section

Temperatures are uncorrected. Ir spectra were obtained with a Beckman IR-8 spectrophotometer. Uv spectra were recorded using a Beckman DB spectrophotometer for solutions prepared from 95% EtOH. Mass spectra were obtained with a Consolidated Electrodynamics Corp. type 21-104 mass spectrometer; an ionizing voltage of 70 eV was used. Nmr spectra were obtained of CCl_4 solutions with a Varian Associates A-60A spectrometer; resonance frequencies were determined relative to 1–2% internal TMS. Vpc chromatograms were obtained with an Aerograph Model A-700 or A-90. Microanalyses were performed at Galbraith Laboratories, Inc., Knoxville, Tenn. Potassium *tert*-butoxide (KO-*t*-Bu) was obtained from MSA Research Corp.

Diethyl 4-Oxa-6-heptyne-1,1-dicarboxylate (1a).—To a stirred solution of 30.6 g (0.19 mol) of 6-bromo-4-oxa-1-hexyne,[6] 161 g (1.0 mol) of diethyl malonate, and 50 ml of PhH was added 4.13 g (0.17 mol) of PhH-washed sodium hydride at 35° in 3 hr. During the addition NaBr precipitated. When the addition was complete, the mixture was heated at 50–55° for 41 hr. The mixture was cooled and filtered, and the filtrate was washed with saturated NaCl (150 ml) and dried ($MgSO_4$). Distillation gave 19.9 g (49%) of the diester: bp 94–96° (0.1 mm); $n^{23}D$ 1.4425; nmr δ 4.21 (q, 4, J = 7.4 Hz, $CO_2CH_2CH_3$), 4.12 (d, 2, J = 2.4 Hz, $OCH_2C{\equiv}C$), 3.58 (t, 2, J = 6.0 Hz, OCH_2CH_2), 3.49 (t, 1, J = 7.2 Hz, CH_2CH), 2.43 (t, 1, J = 2.4 Hz, $\equiv CH$), 2.32–2.05 (m, 2, J = 6.0 and 7.2 Hz, OCH_2CH_2CH), and 1.34 ppm (t, 6, J = 7.4 Hz, OCH_2CH_3).

Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.52; H, 7.43. Found: C, 59.25; H, 7.41.

Reactions of Diethyl 4-Oxa-6-heptyne-1,1-dicarboxylate (1a). A. With Sodium Ethoxide in Ethanol.—To 4.73 g (19.5 mmol) of **1a** was added 15 ml of 1.3 *M* NaOEt in EtOH. The mixture was stirred and heated under reflux for 8 hr. During this time, 20-μl aliquots were taken and analyzed by vpc (SE-30). The reaction mixture was cooled and neutralized with glacial acetic acid, and the resulting mixture was added to 30 ml of ice water and extracted with ether (3 × 30 ml). The ether solutions were combined, washed with saturated NaCl (15 ml), and dried ($MgSO_4$). Analysis by vpc before distillation indicated the presence of 4-carboethoxy-5,6-dihydro-3-methyl-1,4-oxin (**3**) and 4-carboethoxy-2,3,6,7-tetrahydrooxepin (**4**) in a ratio of 1:1.4. Also present were diethyl carbonate, **1a**, and a product with retention time near that of **1a**, which was identified tentatively as diethyl 4-oxa-5,6-heptadiene-1,1-dicarboxylate (**6**). Distillation gave a fraction with bp 46–56° (30 mm) and 45–91° (0.1 mm), which contained 0.70 g (21%) of the dihydrooxin, 1.00 g (30%) of the tetrahydrooxepin, 0.32 g of **1a** and **6**, and 1.70 g (74%) of diethyl carbonate. The components of the mixture were isolated by preparative vpc, and diethyl carbonate and **1a** were identified by comparison with known samples.

3 had $n^{23.5}D$ 1.4561; ir 1730 (vs, C=O), 1665 cm^{-1} (s, C=C); nmr δ 6.19 (q, 1, J = 1 Hz, OCH=), 4.45–3.81 (m, 4, OCH_2CH_3 and OCH_2CH_2CH), 2.80 (t, 1, J = 5 Hz, CH_2CHCO_2), 2.30–1.74 (m, 2, OCH_2CH_2CH), 1.59 (d, 3, J = 1 Hz, $CH{=}CCH_3$), and 1.25 ppm (t, 3, J = 7.5 Hz, OCH_2CH_3); mass spectrum m/e (rel intensity) 170 (12), 97 (100), 69 (10).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.55; H, 8.23. Found: C, 63.89; H, 7.93.

4 had $n^{24}D$ 1.4742; uv λ_{max} 223 mμ (ϵ 6440); ir 1710 (vs, C=O) and 1645 cm^{-1} (m, C=C); nmr δ 7.08 (t, 1, J = 6.0 Hz, C=CH), 4.12 (q, 2, J = 7.2 Hz, OCH_2CH_3), 3.68–3.52 (m, 4, $CH_2CH_2OCH_2CH_2$), 2.78–2.31 (m, 4, $CH_2CH_2OCH_2CH_2$), and 1.28 ppm (t, 3, J = 7.2 Hz, OCH_2CH_3); mass spectrum m/e (rel intensity) 170 (13), 140 (81), 125 (31), 112 (99), 111 (12), 97 (22), 96 (10), 95 (12), 94 (20), 83 (10), 68 (14), 67 (100), 66 (47), 65 (23).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.55; H, 8.23. Found: C, 63.46; H, 8.37.

6 had ir 1950 (C=C=C) and 1730 cm^{-1} (C=O); nmr δ 6.61 (t, J = 6.0 Hz, OCH=C=C), 5.37 (d, J = 6.0 Hz, OCH=C=CH_2), 4.12 (q, J = 7.2 Hz, OCH_2CH_3), 3.54 (t, J = 6.0 Hz,

(7) These reactions are described in the Ph.D. Thesis of J. G. Maroski, University of California, Davis, 1971.

CH_2CH_2O), 3.40 [t, J = 7.0 Hz, $CH(CO_2)_2$], 2.41–1.98 (m, OCH_2CH_2CH), and 1.25 ppm (t, J = 7.2 Hz, OCH_2CH_3). A satisfactory analysis of **6** was not obtained.

A larger scale reaction was carried out for 8 hr. From 28.9 g (0.12 mol) of **1a**, NaOEt prepared from 3.0 g (0.13 g-atom) of sodium, and 130 ml of EtOH was obtained 4.86 g (24%) of **3**, bp 105–106° (19 mm), $n^{24}D$ 1.4562, 3.55 g (18%) of **4**, bp 108–110° (11 mm), $n^{24}D$ 1.4742, 3.91 g of intermediate fractions containing varying amounts of **3** and **4**, and 6.10 g of residue, which contained 1.95 g of **4**, 0.85 g of **6**, and 2.68 g of **1a**. The conversion of **1a** to **3** and **4** was 78%.

B. With Potassium *tert*-Butoxide in Dimethyl Sulfoxide.—A mixture prepared from 11 ml of dry DMSO, 2.35 g (21 mmol) of KO-*t*-Bu, and 5.1 g (21 mmol) of **1a** was heated at 100° for 4 hr and then worked up as described for the reaction with NaOEt in EtOH. Vpc analysis of the ether solution indicated the presence of diethyl carbonate, **3**, **6**, compounds subsequently identified as the *tert*-butyl homolog of **3** and 4-carboethoxy-5,6-dihydro-3-ethoxycarbonylmethyl-1,2-oxin (**5**), and at least three other products which had retention times similar to those of the cyclic products and which were not identified. Distillation gave a 1.2-g fraction, bp 50–65° (0.4 mm), which was estimated by vpc to contain 0.36 g (10%) of **3**, 0.06 g (1.5%) of the *tert*-butyl homolog of **3**, 0.14 g (2.8%) of **5**, and 0.18 g (3.5%) of **6**. These products were isolated by preparative vpc, and **3** and **6** were identified by comparison with previously identified material.

4-Carbo-*tert*-butoxy-5,6-dihydro-3-methyl-1,4-oxin had nmr δ 6.16 (q, J = 1 Hz, OCH=C), 1.61 (d, J = 1 Hz, $OCH{=}CCH_3$), and 1.43 ppm [s, $C(CH_3)_3$].

5 had $n^{23}D$ 1.4705; uv λ_{max} 223 mμ (ε 7380); ir 1735 (vs, unconjugated C=O), 1710 (conjugated C=O), 1655 cm^{-1} (conjugated C=C); nmr δ 4.12 (q, J = 7.0 Hz, $C{=}CCO_2CH_2CH_3$), 4.08 (q, J = 7.0 Hz, $CH_2CO_2CH_2CH_3$), 4.05–4.00 (m, $OCH_2C{=}$), 3.69 (t, J = 5.5 Hz, OCH_2CH_2CH), 3.29 (s, $=CCH_2CO_2$), 2.54–2.20 (m, $OCH_2CH_2C{=}$), 1.26 (t, J = 7.0 Hz, $=CCO_2CH_2CH_3$), 1.23 (t, J = 7.0 Hz, $CH_2CO_2CH_2CH_3$); mass spectrum m/e (rel intensity) 197 (29), 196 (78), 169 (34), 168 (45), 140 (62), 111 (25), 29 (100).

Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.52; H, 7.43. Found: C, 59.36; H, 7.57.

The reaction was repeated using 2.17 g (19.4 mmol) of KO-*t*-Bu and 4.80 g (19.8 mmol) of **1a** except that heating at 100° was maintained for 1 rather than 4 hr. Work-up gave a 2.1-g fraction with bp 45–124° (0.2 mm), which was estimated by vpc to contain 0.20 g (6%) of **3**, 0.08 g (2.1%) of the *tert*-butyl homolog of **3**, 0.47 g (10%) of **5**, and 0.87 g (18%) of **6**.

Registry No.—**1a**, 38858-63-8; **3**, 38858-64-9; **3** *tert*-butyl homolog, 38858-65-0; **4**, 38858-66-1; **5**, 38858-67-2; **6**, 38858-68-3; 6-bromo-4-oxa-1-hexyne, 18668-74-1; diethyl malonate, 105-53-3; sodium ethoxide, 141-52-6; potassium *tert*-butoxide, 865-47-4.

Acknowledgments.—Availability of the mass spectrometer was made possible by a grant from the National Science Foundation. We wish to thank Mr. J. Voth for determination of the mass spectra.

o-Dibenzoyl Heterocycles *via* Cycloaddition Reactions. A Convenient Route to Fused Pyridazine Systems[1]

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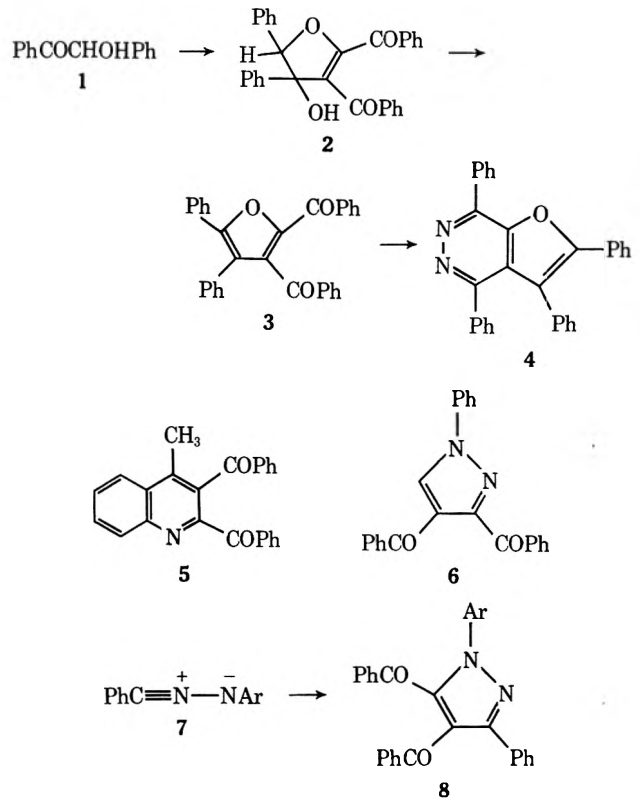
The synthesis of pyridazines from 1,4 diketones and hydrazine hydrate is well-established procedure,[2] its major limitation being the availability of the required 1,4-dicarbonyl precursors. These are especially difficult to obtain in heterocyclic ring systems and this study was undertaken to evaluate cycloaddition procedures as routes to heterocycles with the requisite vicinal dicarbonyl substituents, as well as the final ring closure to the fused pyridazine derivatives themselves.

Utilizing Michael additions[3] as well as a variety of 1,3-dipolar cycloadditions[4] with the acetylenic dipolarophile dibenzoylacetylene, it has been possible to obtain several heterocyclic systems with the requisite substitution pattern. The following reactions illustrate a procedure which should be capable of extension to the synthesis of other heterocycles with analogous substitution patterns.

Condensation of benzoin (**1**) with dibenzoylacetylene in the presence of potassium carbonate gave the hydrated furan **2**, which was readily dehydrated with methanolic hydrochloric acid to 2,3-dibenzoyl-4,5-diphenylfuran (**3**). Treatment of **3** with hydrazine hydrate afforded 2,3,4,7-tetraphenylfuro[2,3-*d*]pyridazine (**4**) in 80% yield. The analytical and spectral data described in Table I and the Experimental Section for this series of products clearly establish their structures.



Similarly, condensation of *o*-aminoacetophenone with dibenzoylacetylene gave 2,3-dibenzoyl-4-methylquinoline (**5**), which was converted into 1,4-diphenyl-10-methylbenzo[*g*[pyrido[2,3-*d*]pyridazine in quantitative yield.

Two isomeric dibenzoylpyrazoles are readily synthesized by 1,3-dipolar cycloaddition techniques. We have recently shown[5] that the reaction of *N*-phenyl-

(1) Support of this work by U. S. Public Health Service Research Grant CA 08495, National Cancer Institute, is gratefully acknowledged.

(2) M. Tisler and B. Stanovnik, *Advan. Heterocycl. Chem.*, **9**, 226 (1968).

(3) J. B. Hendrickson, R. Rees, and J. F. Templeton, *J. Amer. Chem. Soc.*, **86**, 107 (1964).

(4) *E.g.*, see R. Huisgen, H. Gotthardt, and R. Grashey, *Chem. Ber.*, **101**, 536 (1968); K. T. Potts and D. N. Roy, *Chem. Commun.*, 1061, 1062 (1968).

(5) K. T. Potts and D. McKeough, *J. Amer. Chem. Soc.*, **94**, 6215 (1972).

TABLE I
SOME RING-FUSED PYRIDAZINES

Fused pyridazine derived from	Yield, %	Mp, °C	Formula[f]	M·+ (rel intensity)	Uv data, λ_{max}, nm (log ϵ)
2,3-Dibenzoyl-4,5-diphenylfuran	80	203–204[a]	$C_{30}H_{20}N_2O$	424 (100)	222[b] (4.35), 274 (4.25), 310 (4.27)
3,4-Dibenzoyl-1-phenylpyrazole	100	251–252[c,d]	$C_{23}H_{16}N_4$	348 (52)	237 (4.35), 304 (4.38)
4,5-Dibenzoyl-1-(2,4-dibromophenyl)-3-phenylpyrazole	100	224–225[a]	$C_{29}H_{18}Br_2N_4$	580 (66)	224[b] (4.69), 305 (4.14)
2,3-Dibenzoyl-4-methylquinoline	100	240[c,e]	$C_{24}H_{17}N_3$	347 (100)	212 (4.45), 255 (4.64), 360 (3.73)

[a] Colorless needles. [b] Shoulder. [c] Yellow needles from benzene. [d] Nmr ($CDCl_3$) τ 1.27 (s, 1, H_3), 1.1–2.7 (m, aromatic). [e] Nmr ($CDCl_3$) τ 7.30 (s, 3, 10-CH_3), 1.5–2.8 (m, 14, aromatic). [f] Satisfactory analytical values (±0.3 for C, H, and N) were reported for all compounds. Ed.

sydnone with dibenzoylacetylene is a convenient route to 3,4-dibenzoyl-1-1-phenylpyrazole (**6**), and the isomeric system, 4,5-dibenzoyl-1-(2,4-dibromophenyl)-3-phenylpyrazole (**8**), was obtained from the reaction of the nitrilimine[6] **7** with dibenzoylacetylene. Both these pyrazoles underwent ready ring closure with hydrazine hydrate to give the anticipated 2,4,7-triphenylpyrazolo[3,4-*d*]pyridazine and 1-(2,4-dibromophenyl)-3,4,7-triphenylpyrazolo[3,4-*d*]pyridazine, respectively, in quantitative yields (Table I). This ring system has been synthesized previously[7] by ring closure of pyrazine-3,4-dicarboxaldehyde with hydrazine hydrate.

The possibility that these ring-fused pyridazine derivatives would undergo cycloadditions was also of interest. Despite its inherent *o*-quinoidal structure, 3,4,7-triphenylpyrazolo[3,4-*d*]pyridazine did not undergo cycloaddition with *N*-phenylmaleimide and the stability of such systems may be attributed to the introduction of two nitrogen atoms.[8] Thus 2-methyl-2*H*-pyrrolo[3,4-*b*]quinoxaline is a stable entity,[9] whereas 2*H*-naphtho[2,3-*c*]pyrrole can only be trapped as its *N*-phenylmaleimide product.[10] The incorporation of two or more heteroatoms into the five-membered ring may also inhibit the cycloaddition reactions, as naphtho[2,3-*c*][2,1,3]thiadiazole is unreactive toward dienophiles.[11]

Experimental Section[12]

4,5-Dibenzoyl-1-(2,4-dibromophenyl)-3-phenylpyrazole (8, Ar = 2,4-$Br_2C_5H_3$).—*N*-α-Bromobenzylidene-*N'*-(2,4-dibromophenyl)hydrazine[13] (4.33 g, 0.01 mol), dibenzoylacetylene (2.34 g, 0.01 mol), and anhydrous acetonitrile (100 ml) were stirred together at room temperature, and triethylamine (5 ml) was added. After the solution had stirred overnight, the solvent was removed and the residue was washed well with water. Two crystallizations from ethanol gave colorless needles: 60%; mp 174–175°; ir (KBr) 3080, 3045 (CH), 1670, 1650 cm^{-1} (CO); $\lambda_{max}^{CH_3OH}$ 242 nm (sh, log ϵ 4.41), 302 (4.08); nmr ($CDCl_3$) τ 2.9–2.1 (m, aromatic); mass spectrum *m/e* (rel intensity) M·+ 584 (95).

Anal. Calcd for $C_{29}H_{18}Br_2N_2O_2$: C, 59.41; H, 3.10; N, 4.78. Found: C, 59.18; H, 2.94; N, 4.67.

2,3-Dibenzoyl-4,5-dihydro-4,5-diphenyl-4-hydroxyfuran (2).—Benzoin (0.6 g), dibenzoylacetylene (0.7 g), anhydrous sodium carbonate (0.4 g), and dry acetone (20 ml) were boiled together under reflux for 24 hr. The mixture was cooled, poured into water (250 ml), and extracted with ether. The extract was dried ($MgSO_4$), the ether was removed, and the residue was crystallized from methanol (charcoal), forming colorless needles: 39%; mp 171°; ir (KBr) 3500 (OH), 3080, 3045 (CH), 1680 cm^{-1} (CO); $\lambda_{max}^{CH_3OH}$ 255 nm (log ϵ 4.19), 305 (sh, 3.80); nmr ($CDCl_3$) τ 5.77 (s, 1, OH), 4.17 (s, 1, H_5), 2.8–2.0 (m, 20, aromatic); mass spectrum *m/e* (rel intensity) M·+ 446 (27).

Anal. Calcd for $C_{30}H_{22}O_4$: C, 80.70; H, 4.97. Found: C, 80.87; H, 4.96.

2,3-Dibenzoyl-4,5-diphenylfuran (3) was prepared from **2** by the action of boiling methanolic hydrochloric acid during 5 min. Upon concentration the product separated as colorless, matted needles: 100%; mp 157°; ir (KBr) 3080 (CH), 1680 cm^{-1} (CO); $\lambda_{max}^{CH_3OH}$ 256 nm (log ϵ 4.19), 342 (3.68); nmr ($CDCl_3$) τ 2.9–1.8 (m, aromatic); mass spectrum *m/e* (rel intensity) M·+ 428 (100).

Anal. Calcd for $C_{30}H_{20}O_3$: C, 84.09; H, 4.71. Found: C, 84.08; H, 4.64.

2,3-Dibenzoyl-4-methylquinoline (5).—Equivalent amounts of *o*-aminoacetophenone and dibenzoylacetylene were refluxed in methanol for 10 min. On cooling, yellow needles of an adduct were deposited. Without further characterization the product was dissolved in methanolic hydrochloric acid and refluxed for 30 min. Partial removal of the methanol gave a colorless solid which crystallized from benzene as colorless needles: 40%; mp 204–205°; ir (KBr) 3090 (CH), 1680, 1660 cm^{-1} (CO); $\lambda_{max}^{CH_3OH}$ 207 nm (log ϵ 4.62), 255 (4.54); nmr ($CDCl_3$) τ 7.42 (s, 3, CH_3), 2.8–1.6 (m, 14, aromatic); mass spectrum *m/e* (rel intensity) M·+ 351 (58).

Anal. Calcd for $C_{24}H_{17}NO_2$: C, 82.03; H, 4.88; N, 3.99. Found: C, 82.37; H, 4.66; N, 3.85.

Ring-Fused Pyridazines.—The following method illustrates the general procedure used. The dibenzoyl compound was dissolved in the minimum quantity of boiling ethanol, hydrazine hydrate (85%, twofold excess) was added, and the solution, after refluxing for 15 min, was filtered and allowed to cool, whence the products described in Table I separated.

Registry No.—**1**, 119-53-9; **2**, 38974-10-6; **3**, 38899-31-9; **4**, 38899-32-0; **5**, 38899-33-1; **6**, 37687-10-8; **8** (Ar = 2,4-$Br_2C_6H_3$), 38899-35-3; 1,4-diphenyl-10-methylbenzo[*g*]pyrido[2,3-*d*]pyridazine, 38899-36-4; 2,4,7-triphenylpyrazolo[3,4-*d*]pyridazine, 38974-11-7; 1-(2,4-dibromophenyl)-3,4,7-triphenylpyrazolo[3,4-*d*]-pyridazine, 38899-37-5; *N*-α-bromobenzylidine-*N'*-(2,4-dibromophenyl)hydrazine, 2516-46-3; dibenzoylacetylene, 1087-09-8; *O*-aminoacetophenone, 551-93-9.

(6) R. Huisgen, *Proc. Chem. Soc.*, 357 (1961).
(7) C. V. Greco, F. C. Pellegrini, and M. A. Pesce, *J. Heterocycl. Chem.*, **9**, 967 (1972).
(8) D. W. H. MacDowell, A. T. Jeffries, and M. B. Meyers, *J. Org. Chem.*, **36**, 1416 (1971).
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The Synthesis of Some 2,2′-Dioxa-Bridged Biphenyls and 1,1′-Binaphthyls[1a]

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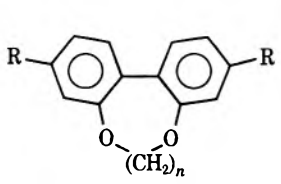
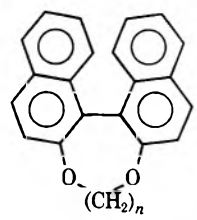
In the course of a study involving the synthesis and evaluation as liquid scintillator solutes of a number of bridged *p*-quaterphenyls of the type **1** it was necessary to prepare a number of 2,2′-bridged biphenyls (**2**). The 2,2′-bridged 1,1′-binaphthyls (**3**) were also of interest to us as scintillators and their synthesis is reported here along with the biphenyl derivatives (**2**).





1, R = C_6H_5; n = 1, 2, 3, 4
2a, R = H; n = 1
b, R = H; n = 2
c, R = H; n = 3
d, R = H; n = 4

3a, n = 1
b, n = 2
c, n = 3
d, n = 4

The dioxepins (**a**), dioxocins (**b**), dioxonins (**c**), and dioxecines (**d**) in the biphenyl series (**2**) and 1,1′-binaphthyl series (**3**) were each obtained from 2,2′-dihydroxybiphenyl (**4**) and 1,1′-bi-2-naphthol (**5**), respectively. In each case, depending on the desired number of methylenes in the bridge, a solution of methylene iodide, 1,2-dibromoethane, 1,3-dibromopropane, or 1,4-dibromobutane in anydrous *N*,*N*-dimethylformamide (DMF) was added to a heated mixture of the appropriate dihydroxy compound and potassium carbonate in anhydrous *N*,*N*-dimethylformamide to yield the folowing: dibenzo[*d*,*f*][1,3]dioxepin (**2a**), 6,7-dihydrodibenzo[*e*,*g*][1,4]dioxocin (**2b**), 7,8-dihydro-6*H*-dibenzo[*f*,*h*][1,5]dioxonin (**2c**), 6,7,8,9-tetrahydrodibenzo[*g*,*i*][1,6]dioxecine (**2d**), dinaphtho[2,1-*d*:1′,2′-*f*][1,3]dioxepin (**3a**), 4,5-dihydrodinaphtho[2,1-*e*:1′,2′-*g*][1,4]dioxocin (**3b**), 5,6-dihydro-4*H*-dinaphtho[2,1-*f*:1′,2′-*h*][1,5-]dioxonin (**3c**), and 4,5,6,7-tetrahydrodinaphtho[2,1-*g*:1′,2′-*i*][1,6]dioxecine (**3d**). See Table I.

Thus, the yields of the bridged ethers in the biphenyl series (**2**) were superior to those reported recently[2] in which the diol was treated with sodium hydroxide and the appropriate dihalide in aqueous dimethyl sulfoxide. In all cases the biphenyl derivatives **2a**–**2d** obtained in our work had physical properties and ultraviolet absorption spectra essentially identical with those reported.[2,3] The compounds **3a**, **3c**, and **3d** are new compounds and the dioxocin **3b** had physical properties in agreement with those previously reported.[4]

TABLE I

DIOXA-BRIDGED BIPHENYLS AND BINAPHTHYLS[a]

Compd	Time[f]	Temp, °C	Yield, %	Mp, °C
2a	1.0 (18)	80–90	56	36.5–37.5 (reported[g] 35–36)
2b	2.5 (16)	90–100	38	97.8[b] (reported[g,h] 98)
2c	5.0 (15)	100–110	53	72.5–73.5[b] (reported[g] 67–69)
2d	6.0 (14)	75–80	38	109–110[c] (reported[g] 110–111)
3a	1.0 (4)	100–110	52	178.5–179.5[d]
3b	7.0 (14)	75–85	7	197–198.5[d] (reported[i] 196–197)
3c	3.0 (18)	80–90	49	272.5–273.5[e]
3d	3.0 (18)	80–90	76	256.5–257.5[e]

[a] Analytical samples of all of the compounds reported here gave satisfactory analytical data (±0.4% for C and H). All products were chromatographed in benzene or cyclohexane–benzene over Woelm neutral activity grade I alumina prior to recrystallization. [b] Recrystallization solvent was petroleum ether (bp 30–60°). [c] Recrystallization solvent was petroleum ether (bp 60–90°). [d] Recrystallization solvent was cyclohexane–benzene. [e] Recrystallization solvent was benzene. [f] Time of addition of halide in hours (time of heating in hours after addition). [g] D. W. Allen, P. N. Braunton, I. T. Millar, and J. C. Tebby, *J. Chem. Soc. C*, 3454 (1971). [h] O. Diels and A. Bibergeil, *Ber.*, **35**, 302 (1902). [i] M. R. Fosse, *Bull. Soc. Chim. Fr.*, **19**, 611 (1898).

Experimental Section

All melting points were taken in Pyrex capillary tubes in a Hoover-Thomas melting point apparatus and are uncorrected. Ultraviolet absorption spectra were taken in cyclohexane solution and were run on a Cary Model 14 spectrophotometer.

General Procedure.—The preparation of dibenzo[*d*,*f*][1,3]-dioxepin (**2a**) is described in detail, and the synthesis of the other compounds was carried out in a similar fashion.

Dibenzo[*d*,*f*][1,3]dioxepin (2a).—A solution of 2.95 g (0.011 mol) of methylene iodide in 35 ml of DMF was added dropwise over 1.0 hr to a stirred mixture of 1.86 g (0.01 mol) of 2,2′-dihydroxybiphenyl (**4**), mp 108–110°, and 3.04 g (0.022 mol) of anhydrous potassium carbonate in 50 ml of DMF maintained between 80 and 90°. After the reaction mixture has been heated for an additional 18 hr, it was poured into water and extracted with ether, and the ether layer was washed with 5% sodium hydroxide and water. The ether layer was dried (K_2CO_3), the solvent was removed on a steam bath, and the residue was chromatographed from a 10:1 cyclohexane–benzene solution through a Woelm alumina column (neutral activity, grade I). Removal of the solvent left an oil which solidified upon cooling; after several unsuccessful crystallization attempts, the solid was evaporatively distilled (90°, 0.05 Torr) yielding 1.1 g (56% yield) of dibenzo[*d*,*f*][1,3]dioxepin (**2a**) as a colorless solid, mp 36.5–37.5°.

Registry No.—**2a**, 220-11-1; **3a**, 188-35-2; **3c**, 38896-36-5; **3d**, 38896-37-6; **4**, 1806-29-7.

(1) (a) From the dissertation presented by J. Ernest Simpson to the graduate faculty of the University of New Mexico in partial fulfillment of the requirements for the degree of Doctor of Philosophy. This investigation was supported in part by a Research Grant from the Division of Biology and Medicine of the U. S. Atomic Energy Commission, Contract No. AT(29-2)-915. (b) Graduate Research Assistant, June 1963 to August 1967. (c) Work performed under the auspices of the U. S. Atomic Energy Commission.

(2) D. W. Allen, P. N. Braunton, I. T. Millar, and J. C. Tebby, *J. Chem. Soc. C*, 3454 (1971).

(3) P. N. Braunton, I. T. Millar, and J. C. Tebby, *J. Chem. Soc., Perkin Trans. 2*, 138 (1972).

(4) M. R. Fosse, *Bull. Soc. Chim. Fr.* **19**, 611 (1898).

Communications

See Editorial, *J. Org. Chem.*, **37**, No. 19, 4A (1972).

Concertedness: a Function of Dynamics or the Nature of the Potential Energy Surface?

Summary: Whether or not a given reaction is concerted depends on molecular size and reaction conditions as well as the depth of local potential energy minima between reactant and product wells; any proposed quantitative definition of concertedness must, therefore, stress maximum lifetimes of potential intermediates in relation to molecular size and reaction conditions.

Sir: The orbital symmetry approach[1] to chemical reactivity recognizes only two types of reaction channel: allowed (symmetry correlation of all bonding reactant molecular orbitals with bonding product molecular orbitals) and forbidden (symmetry correlation of at least one bonding reactant orbital with one antibonding product orbital). To fully explore the limits of this theory, and also to escape irrefutability,[2] would require a quantitative definition of concertedness.[3]

Thus, the question has been posed:[6] Should some time limit (say 10^{-12} sec) be defined as the maximum allowable lifetime for intermediates in concerted cycloreactions, or should concertedness rely on the fact that no potential energy well on the hypersurface connecting reactant and product exceeds some maximum depth (say $^1/_2 h\nu_0$)?

It is the intention here to pursue two theoretical points initially raised by Wolfgang[7,8] which lead to the conclusions that a reaction is a one-step process when (1) there are no potential energy minima between reactant and product wells, (2) there is an energy minimum on the reaction coordinate, but the reacting system contains too few atoms to exist as an intermediate complex, or (3) a potential well separates reactant and product wells but the reacting system possesses a large internal energy such that in the absence of collisional deactivation the intermediate complex is unstable and transforms directly into product.

While it is well-known that an energetically concerted reaction,[9] characterized by a potential energy surface in configuration space with no energy minima between reactant and product wells, is a one-step process, it is not generally appreciated that a potential energy hypersurface containing a distinct potential energy minimum on the way to product may correspond to either a one-step or two-step process[10] depending on the depth of the well, the density of energy states available to the intermediate, and the activation imparted to the reacting system.[11]

The actual experimental differentiation of a transition state from a true intermediate remains a fundamental problem in "reaction spectroscopy." The lifetime (τ) of a transition state is given by the reciprocal sum of all rate constants which lead to decay, one vibration leading to product and another leading to reactant, each approximately 10^{13} sec^{-1}: $\tau_{TS} = 5 \times 10^{-14}$ sec.

From Rice–Ramsperger–Kassel (RRK) theory[12,13] one can obtain an estimate of the requirements for formation of an intermediate in a thermally activated reaction.[8] The rate constant, k_ϵ, for unimolecular decay of a vibrationally excited molecule of internal energy ϵ is given by eq 1, where ϵ^* is the minimum activation

$$k_\epsilon = A[(\epsilon - \epsilon^*)/\epsilon]^{s-1} \quad (1)$$

energy for spontaneous decay (see Figure 1) and s is the number of "active" vibrational modes. A more accurate RRK equation (2) only allows two-thirds of

$$k_\epsilon = A[(\epsilon - \epsilon^*)/\epsilon]^{2N-5} \quad (2)$$

the total number of vibrational modes to be active; *i.e.*, $s = {}^2/_3(3N - 6) = 2N - 4$ for a nonlinear N-atomic molecule. The lifetime follows from eq 2 with

$$\tau_\epsilon = 1/k_\epsilon = [(\epsilon - \epsilon^*)/\epsilon]^{5-2N} \times 10^{-13} \text{ sec}$$
$$\tau_\epsilon = [1 - (\epsilon^*/\epsilon)]^{5-2N} \times 10^{-13} \text{ sec} \quad (3)$$

(1) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969); "The Conservation of Orbital Symmetry," Academic Verlag Press, 1970.

(2) If all allowed reactions were assumed to be concerted, and similarly all forbidden reactions were nonconcerted when observed, then a failure to observe the orbital-symmetry-predicted reaction stereochemistry could be interpreted as either a violation of the theory or as a nonconcerted reaction. Hence, the theory could never be refuted, unless concertedness is placed on a quantitative basis and uncoupled from allowedness. Consideration of electronic state symmetry and configuration interaction has lead to a theoretical uncoupling of concertedness and orbital symmetry: J. E. Baldwin, A. H. Andrist, and R. K. Pinschmidt, Jr., *Accounts Chem. Res.*, **5**, 402 (1972).

(3) A reaction is generally considered to be "concerted" if the transition state is characterized by (1) equal bond making and bond breaking for unimolecular isomerization, (2) equal bond breaking at two reaction termini in a cycloelimination, or (3) equal bond making at the reaction termini in a cycloaddition. (An analogous definition based on the synchroneity of bond cleavage and formation is also frequently employed.) Such bond breaking aided by bond making should require a lower activation energy than the corresponding dissociation–recombination process. Since the most elusive molecular property (which is even more elusive for transition states) is the distribution of electrons,[4] concertedness has defied quantification in an empirical sense.[5]

(4) *Cf.* W. H. Flygare, *Science*, **140**, 1179 (1963).

(5) *Cf.* S. H. Bauer, *J. Amer. Chem. Soc.*, **91**, 3688 (1969).

(6) Informal discussions, 14th Conference on Reaction Mechanisms, University of Vermont, Burlington, Vt., June 13–16, 1972.

(7) R. Wolfgang, *Accounts Chem. Res.*, **2**, 248 (1969).

(8) R. Wolfgang, *Accounts Chem. Res.*, **3**, 48 (1970), and references therein.

(9) J. E. Baldwin and R. H. Fleming, *Fortsch. Chem. Forschung*, **15**, 281 (1970).

(10) It would not be inconsistent for such a two-step, energetically nonconcerted process simultaneously to be bondingly and orbitally concerted.[9]

(11) While this conclusion has its most direct applications to reactions in the gas phase, it surely applies whenever collisional deactivation is unable to compete with progress along the reaction coordinate.

(12) Qualitative estimates based on RRK theory have, on the whole, been fully substantiated within the refined Rice–Ramsperger–Kassel–Marcus (RRKM) theory; *cf.* H. S. Johnston, "Gas Phase Reaction Rate Theory," Ronald Press, New York, N. Y., 1966; G. L. Pratt, "Gas Kinetics," Wiley, New York, N. Y., 1969; and P. J. Robinson and K. A. Holbrook, "Unimolecular Reactions," Wiley-Interscience, New York, N. Y., 1972.

(13) Professor R. G. Bergman has pointed out that the use of exact A factors and the expanded equation given by Setser and Rabinovitch[14] leads to improved estimates of *absolute* rate constants, but the method is not so easily applied as the modified RRK approach used here since zero-point energies of the energized molecule and the activated complex are required.

(14) D. W. Setser and B. S. Rabinovitch, *Can. J. Chem.*, **40**, 1425 (1962).

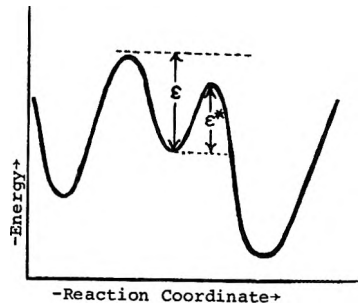


Figure 1—Energy *vs.* reaction coordinate diagram illustrating ϵ and ϵ^*.

inclusion of a "normal" A factor.[8] If a true intermediate, as opposed to a transition state, must have $\tau \geqslant 10^{-12}$ sec, then eq 4 obtains. Table I lists minimum

$$\epsilon^*/\epsilon = 1 - 10^{x/(5-2N)} \quad (x \geqslant 1.0) \qquad (4)$$

TABLE I
VALUES OF ϵ^*/ϵ *vs.* N FROM EQ 4 WITH $x = 1.0$

N	3	4	5	9	14	52
ϵ^*/ϵ	0.90	0.54	0.37	0.16	0.10	0.02

values of ϵ^*/ϵ which allow an intermediate to exist with $\tau = 10^{-12}$ sec *vs.* N calculated from eq 4; Figure 2 gives the corresponding plot of ϵ^*/ϵ *vs.* N.

An interesting result is revealed by the plot in Figure 2. As the number of atoms increases, the activation energy required to contain an intermediate for 10^{-12} sec falls off rapidly for any given internal energy. For example, a 27.0-kcal mol^{-1} activation energy is required to contain a 4-atom transient with 50 kcal mol^{-1} internal energy, while a mere 5.0-kcal mol^{-1} barrier will contain a 14-atom intermediate of the same internal energy for 10^{-12} sec.

Equation 4 and the plot in Figure 2 reflect the principle that the density of vibrational states increases directly with molecular size, and it is precisely this larger density of vibrational states which permits the complex molecule to form an intermediate while experiencing only a small barrier against spontaneous decomposition.

This conclusion forces a consideration of substituent effects on molecular rearrangements: Can the replacement of small groups with large groups make some nonconcerted reaction channel competitive with an otherwise dominant concerted path? Paquette and Epstein have suggested that replacement of two hydrogens with two phenyl groups perturbs the parent bicyclo[5.2.0]-nona-2,5,8-triene system too severely to establish any mechanistic analogy.[15] This effect may contribute to the documented reactivity differences between ketene and diphenylketene,[16] 2,3,3,4-tetramethyl- and 2,4-diphenyl-3,3-dimethyltricyclo[3.2.0.^{2,4}0^{1,5}]hept-6-ene,[17] *meso*-3,4-dimethyl- and *meso*-3,4-diphenylhexa-1,5-diene,[18,19] and allene and phenyl-substituted allenes.[20]

(15) L. A. Paquette and M. J. Epstein, *J. Amer. Chem. Soc.*, **93**, 5936 (1971).

(16) J. E. Baldwin and J. A. Kapecki, *J. Amer. Chem. Soc.*, **92**, 4868 (1970), and references cited.

(17) L. A. Paquette and L. M. Leichter, *J. Amer. Chem. Soc.*, **92**, 1765 (1970); *ibid.*, **93**, 4922, 5128 (1971).

(18) W. von E. Doering and W. R. Roth, *Tetrahedron*, **18**, 67 (1962).

(19) R. P. Lutz, S. Bernal, R. J. Boggio, R. O. Harris, and M. W. McNicholas, *J. Amer. Chem. Soc.*, **93**, 3985 (1971); see also M. J. S. Dewar and L. E. Wade, *ibid.*, **95**, 290 (1973).

(20) J. E. Baldwin and L. E. Walker, *J. Org. Chem.*, **36**, 1440 (1971), and references cited.

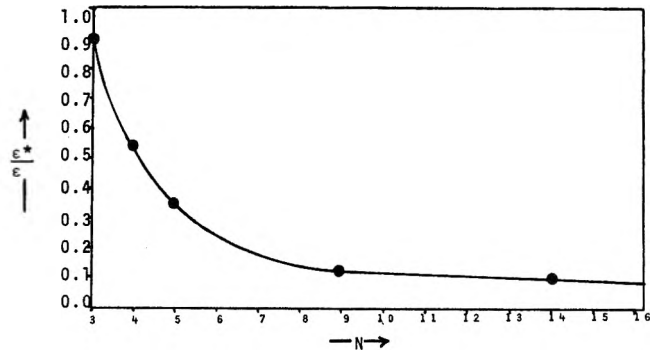


Figure 2—Plot of ϵ^*/ϵ *vs.* N from Table I.

Whether a given energized molecule may pass directly over a potential well separating it from isolable product while maintaining its internal energy above ϵ^* depends on the third parameter in eq 4, ϵ, and what opportunities for collisional deactivation may be present. Molecular beam experiments[8] on the energy dependence of bimolecular reactions have demonstrated the actual conversion of two-step, energetically nonconcerted reactions into one-step, fully concerted processes at higher internal energies.[21] Thus, even if a potential well of sufficient depth presents an opportunity for intermediate formation, it does not require that such an intermediate be formed![22,25]

In conclusion, concertedness depends not only on the nature of the potential energy surface itself, but also the motion of the system on this surface. Any empirical definition of concertedness which is adopted must focus on the dynamics of the reacting system and not simply intermediate potential well depth. Experiments aimed at distinguishing concerted from diradical or nonconcerted cycloreactions would be more meaningfully directed toward establishing maximum lifetimes of potential intermediates as a function of molecular size and reaction conditions.

Acknowledgment.—Helpful discussions with Professors John E. Baldwin and Robert G. Bergman are gratefully acknowledged.

(21) At higher ϵ it becomes more difficult to transfer the energy of reaction into internal vibrational modes.[8] Contrast this situation with chemical activation of stable species: B. S. Rabinovitch and M. C. Flowers, *Quart. Rev. (London)*, **18**, 122 (1964).

(22) Intermediate situations have been rationalized through a superposition of "quasiconcerted" processes[23] and as a broad, flat plateau on the potential energy surface termed a "twixtyl".[24]

(23) J. P. Freeman, D. G. Pucci, and G. Binsch, *J. Org. Chem.*, **37**, 1894 (1972).

(24) R. Hoffmann, S. Swaminathan, B. G. Odell, and R. Gleiter, *J. Amer. Chem. Soc.*, **92**, 7091 (1970).

(25) Intermediate formation is not so easily avoided at higher ϵ when a "spin barrier" is present; *cf.* L. M. Stephenson and J. I. Brauman, *J. Amer. Chem. Soc.*, **93**, 1988 (1971).

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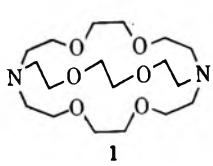
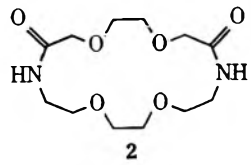
Flow Synthesis. A Substitute for the High-Dilution Steps in Cryptate Synthesis

Summary: Certain cyclization reactions, usually run under conditions of high dilution over long periods of time, give excellent yields in <1 min when the reagents are efficiently mixed in a suitable flow cell.

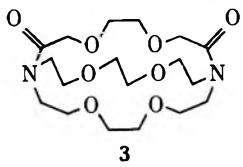
Sir: In a recent synthesis of the polyoxa macrobicyclic diamine, **1**, which forms cage complexes (cryptates) with alkali and alkaline earth cations[1-3] and which can be used to dissolve alkali metals in amines and ethers,[4,5] we followed essentially the procedure of Dietrich, Lehn, and Sauvage.[1,6] Synthesis of both of the intermediates, **2** and **3**, from the appropriate di-



1



2



3

amine and diacid chloride used the high-dilution method recommended by Stetter and Marx.[7] Similar procedures were used by Simmons and Park[8,9] in the synthesis of diazabicycloalkanes and by Lehn and coworkers[10-13] in their continuing synthesis of a number of macrobicyclic and macrotricyclic ligands.

The recommended procedure requires the slow addition with vigorous stirring (over a period of ~8 hr) of dilute (~0.1 *M*) solutions of the two reagents in benzene into a reaction flask under a nitrogen atmosphere. We found that the yields were not greatly reduced by speeding up the addition process, provided that the stirring was sufficiently vigorous. This suggested that the most important factor in these reactions is efficient stoichiometric mixing. This supposition was tested by using a flow cell to carry out these steps.

The mixing chamber is of the type used in our laboratory for stopped-flow kinetics studies.[14,15] It has four tangential 1.0-mm inlets "drilled" into a 2.0-mm-i.d. Pyrex capillary. An Airbrasive unit (S. S. White Co.), which uses helium to drive Alundum through a nozzle at supersonic velocities, was used to make the inlet holes. (Presumably, conventional mixing chambers made of Teflon or metal could be used.) The reactant solutions were driven through the mixing chamber at flow velocities high enough to ensure turbulent mixing by applying about 3 atm of nitrogen pressure to the stock solutions. The heavy-walled vessels which contained the stock solutions were connected to the mixing chamber with 5-mm Solv-Seal joints (Fischer-Porter Co.) through Teflon needle-valve stopcocks (Kontes). The entire apparatus was surrounded by a metal safety shield.

Completion of the reaction between an amine and an acid chloride requires a base to remove the HCl formed. In the high-dilution method, either a 2:1 ratio of diamine to diacid chloride is used or else a tertiary amine such as triethylamine is used to scavenge HCl. However, in the formation of both **2** and **3**, we have found that triethylamine reduces the yield substantially. With the flow technique the required excess of amine may either be present in the amine stock solution or it may be in the receiver flask. The amine hydrochloride is removed by filtration and reconverted to the amine with very little net loss of material.

In a typical flow reaction, 200 ml of a 0.06 *M* solution of the diamine and 200 ml of a 0.03 *M* solution of diacid chloride in benzene were allowed to flow through the flow cell. The total flow time was ~10 sec. Higher concentrations of reagents tended to cause blockage of the flow tube by the precipitated amine hydrochloride. The amine hydrochloride was removed by filtration and the dilactam, **2**, was recovered by removing the solvent in a rotary evaporator and purified by elution through an alumina column with benzene (mp 108–109°; pmr singlet at 3.90, multiplet at 3.50 ppm). The purified yield was 70% which is the same as the yield obtained for similar concentrations by the high-dilution method. Similar results were obtained in the synthesis of the bicyclic lactam, **3**. In all cases the yield was sensitive to the purity of the diacid chloride which is susceptible to decomposition upon vacuum distillation. Recrystallization from a mixture of ether and petroleum ether as recommended by Lehn[6] yields a pure product which can be stored for weeks at −10° without decomposition.

Consideration of the kinetics to be expected in cyclization reactions suggests the requirements which must be met if the flow method is to be a useful replacement for high-dilution techniques. (1) Mixing must be rapid and complete so that the proper stoichiometry is maintained. (2) The initial step in the reaction must be fast enough to be substantially complete during the time of flow. (3) The cyclization step must be fast enough to compete with intermolecular reactions. It is likely that the type of reaction considered in this paper meets criteria 2 and 3 by the rapid formation of a cyclic acid–base complex or hydrochloride salt. The fact that the HCl scavenger may be placed in the receiver flask shows that it need not be present at the point of initial reaction. The precipitation of an amine hydrochloride in the flow tube shows that the reaction proceeds at least to this point in <10 msec.

Flow synthesis should be readily applicable to other than cyclization reactions. It would be a simple matter to add another mixer for sequential reactions or for the quenching of undesirable reactions. If the reaction of interest is fast and the products are sensitive to decomposition or secondary reactions under the conditions of the experiment, then we would expect flow methods to be applicable. The simplicity of the apparatus makes the method attractive for routine laboratory use.

(1) B. Dietrich, J. M. Lehn, and J. P. Sauvage, *Tetrahedron Lett.*, 2885, 2889 (1969).
(2) J. M. Lehn, J. P. Sauvage, and B. Dietrich, *J. Amer. Chem. Soc.*, **92**, 2916 (1970).
(3) J. M. Lehn and J. P. Sauvage, *Chem. Commun.*, 440 (1971).
(4) J. L. Dye, M. T. Lok, F. J. Tehan, R. B. Coolen, N. Papadakis, J. M. Ceraso, and M. DeBacker, *Ber. Bunsenges. Phys. Chem.*, **75**, 659 (1971).
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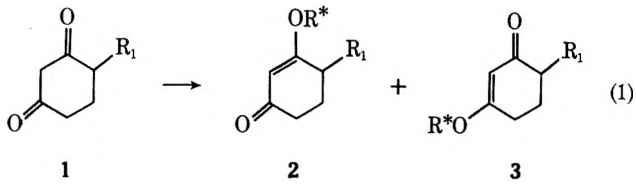
The Regiospecific Alkylation of Cyclic β Diketone Enol Ethers. A General Synthesis of 4-Alkylcyclohexenones

Summary: The alkylation of the kinetic enolate derived from 3-alkoxycyclohexenones is shown to take place in high yield at C_6, thus leading to a general synthesis of 4-alkyl-2-cyclohexenones free of double-bond isomers.

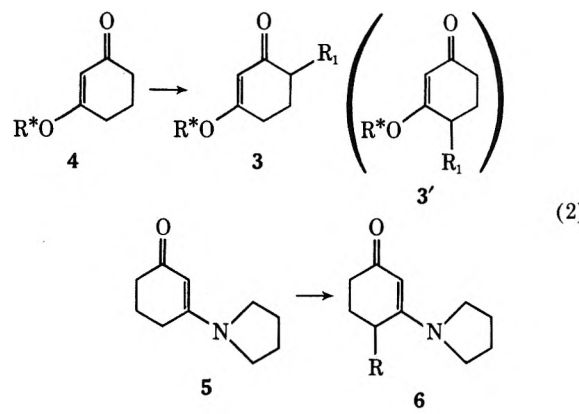
Sir: Enol ethers of cyclic β diketones are very valuable synthetic intermediates, *e.g.*, in the construction of cyclohexenones.[1] Unfortunately, there is no general method for the regiospecific formation of a given enol ether when the starting diketone is unsymmetrical. In such a situation, enol ether formation leads to mixtures of the two possible products (*cf.* **1** → **2** and **3**, eq 1).



1 **2** **3** (1)

We now wish to present a solution to this problem which should greatly extend the utility of cyclic β diketones as synthetic intermediates: We have found that monoalkylation of the enol ether of symmetrical cyclic β diketones, *e.g.*, **4**, can be effected regiospecifically to give **3**, a result especially noteworthy as the alkylation of the related enamine has recently been reported to follow a different course (*e.g.*, **5** → **6**,[2] eq 2).

The alkylations are especially clean with reactive (allylic) halides. For instance, the lithium enolate (made at −78° in tetrahydrofuran with lithium diisopropylamide) of **4** (R* = isobutyl[3]) was treated with 1.1 equiv of allyl bromide, finally at room temperature, to yield, in almost quantitative yield, the monoallylated product (**7**) of **3** (R* = isobutyl; R_1 = allyl), needles of mp 37–38°. The gross structure was only compatible with either **3** or **3′** because of the mass spectrum (*m/e* 208) and the obvious presence of one allyl residue in the

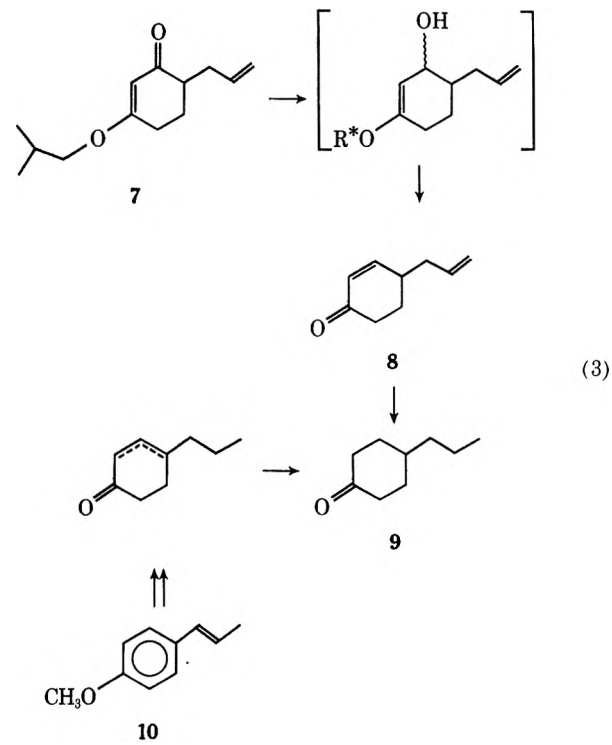


4 **3** **3′** (2) **5** **6**

nmr, which retained the vinyl hydrogen of the enone system as a singlet at δ 5.3.

The correctness of structure **3** was demonstrated by a sequence which also serves to illustrate one of the important uses of substances of this type, the *synthesis of pure 4-alkyl-Δ²-cyclohexenones*, essentially free from the (usually) more stable Δ³ isomer. Lithium aluminum hydride reduction (refluxing ether) and hydrolysis (2 *N* hydrochloric acid, 30-min stirring, room temperature), gave, in ~80% overall yield from **4**, 4-allyl-2-cyclohexenone (**8**, eq 3), bp 87–88° (7 mm), *m/e* 136.0863, free of β,γ isomer as shown by the nmr (1 H split doublet at δ 7.0 due to the β hydrogen of the α,β system) and the ir absorption at 5.93 μ.

Catalytic hydrogenation of **8** (10% Pd/C in ethanol) gave 4-propylcyclohexanone **9**, identical (by glc on 5% SE-30, 100°, and ir) with an authentic sample made from anethole (**10**) by the sequence Birch reduction (lithium–ammonia–methanol), hydrolysis (3 *N* hydrochloric acid–aqueous methanol), and hydrogenation of the α,β–β,γ mixture of 4-propylcyclohexenones (eq 3).



7 **8** (3) **9** **10**

It is especially remarkable and synthetically useful that proton transfer reactions between the initial lithium enolates of 1,3 diketone enol ethers (*e.g.*, of **4**) and the monoalkylated product (*e.g.*, **3**) are extremely

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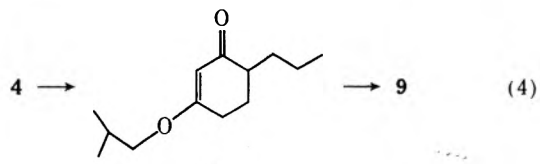
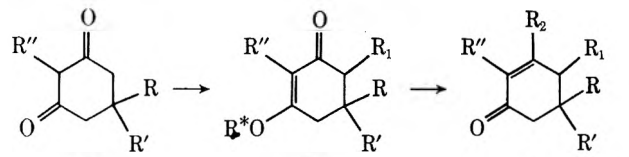
slow, thus leading to excellent yields of monoalkylated products, in spite of the rather slow alkylation of these lithium enolates in tetrahydrofuran.

The low reactivity of the lithium enolate of **4** (R* = isobutyl) in tetrahydrofuran, presumably due to aggregation, is illustrated by the fact that, using propyl bromide under the same conditions which lead to almost quantitative alkylation with allyl bromide, only starting enol ether is recovered. It is, however, possible to achieve alkylation by the use of alkyl iodides in the presence of some hexamethylphosphoramide. Thus, under the same condition as with allyl bromide, but in the presence of 1.1 equiv of hexamethylphosphoramide, **4** (R* = isobutyl) gave with 1 equiv of propyl iodide, in 24 hr at room temperature, a mixture consisting of 65% **11**, (eq 4), in addition to 29% starting enol ether and ~6% dialkylated material.[4]



11 (4)

The alkylation of enol ethers derived from symmetrical cyclohexane-1,3-diones can lead to a great variety of cyclohexenone derivatives. Starting with readily available cyclohexane 1,3-diones such as **12** in which R, R′, and R″ are either H or alkyl (aryl), the sequence involving alkylation of the corresponding enol ether with R_1X leads first to **13** and then, *via* either lithium aluminum hydride reduction or Grignard addition followed by hydrolysis, to cyclohexenones **14** in which R_1 = alkyl and R, R′, R″, and R_2 are either alkyl, aryl, or hydrogen (eq 5).



12 **13** **14** (5)

The procedure for the large scale synthesis of **7** is given in detail. **4** (R* = isobutyl) (84.1 g) in 125 ml of dry tetrahydrofuran was added over 1.5 hr at −78° under nitrogen to a solution containing ~1 equiv of lithium diisopropylamide (made *in situ* at −20° from 229 ml of 2.29 *M* *n*-butyllithium and 55.8 g of diisopropylamine). After 45 min, a solution of 66.5 g of allyl bromide in 100 ml of tetrahydrofuran was added over 20 min. The solution was allowed to warm to room temperature in ~4 hr, 5 ml of water was added, and the solvent was evaporated. Extraction and work-up as usual gave 103.5 g (~98%) of **7**, pure by tlc (15% ethyl acetate–benzene on silica gel), which crystallized on standing in long colorless needles, mp 37–38° after crystallization from ether–acetone at Dry Ice temperature.

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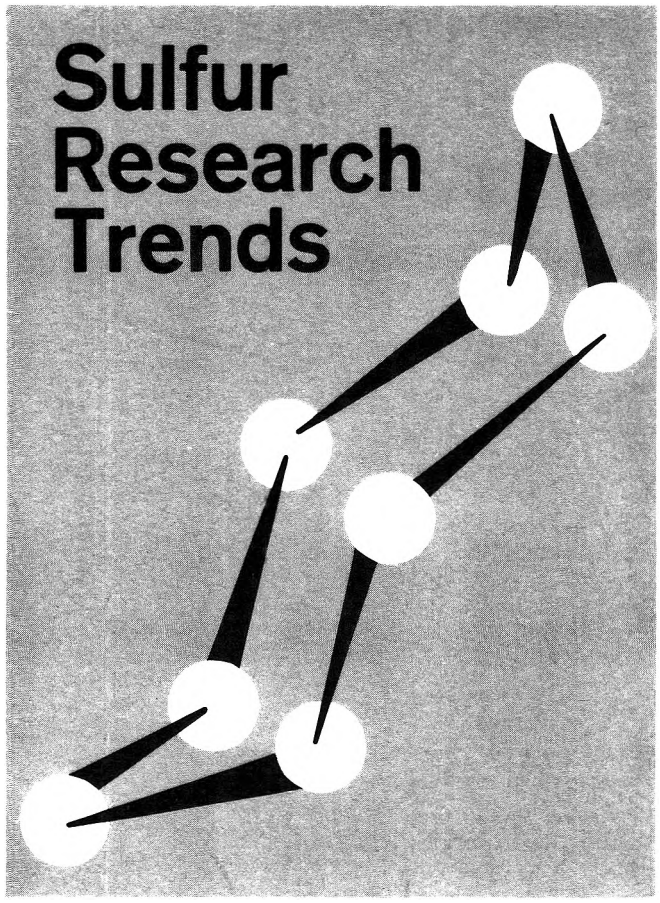
(4) These products could be separated by silica gel chromatography which gave (benzene, then benzene–ethyl acetate) starting material, followed by the dialkylated product, and finally the monoalkylated product **11**. Retention times, on a 10-ft. 2% Carbowax column at 148°, were ~3, 7, and 5 min, respectively. Structures followed from direct comparison and mass, nmr, and ir spectra. The monoalkylated compound **11** was also converted (*cf.* **7** → **9**) to 4-propylcyclohexanone (**9**).



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1. H.C. Brown and S. Krishnamurthy, *J. Amer. Chem. Soc.*, **95**, 1669 (1973).

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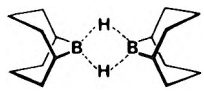

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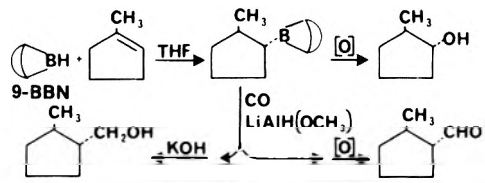

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